



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 471/04, A61K 31/44, 31/505, 31/52, C07D 487/04		A1	(11) International Publication Number: WO 99/40091
			(43) International Publication Date: 12 August 1999 (12.08.99)
(21) International Application Number: PCT/US99/02500		(74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).	
(22) International Filing Date: 5 February 1999 (05.02.99)			
(30) Priority Data:		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
60/073,927 6 February 1998 (06.02.98) US 60/073,981 6 February 1998 (06.02.98) US 60/093,482 20 July 1998 (20.07.98) US 60/093,577 20 July 1998 (20.07.98) US 09/246,775 4 February 1999 (04.02.99) US			
(71) Applicant: AMGEN INC. [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).			
(72) Inventors: NORMAN, Mark, H.; 3038 Shadow Hill Circle, Thousand Oaks, CA 91360 (US). CHEN, Ning; 2888 Capella Way, Thousand Oaks, CA 91362 (US). HAN, Nianhe; 2217 Rutland Place, Thousand Oaks, CA 91362 (US). LIU, Longbin; 753 Rushing Creek Place, Thousand Oaks, CA 91320 (US). HURT, Clarence, R.; 269 Camino Toluca, Camarillo, CA 93010 (US). FOTSCH, Christopher, H.; 533 Timberwood Avenue, Thousand Oaks, CA 91360 (US). JENKINS, Tracy, J.; 391 Country Club Drive #16, Simi Valley, CA 93065 (US). MORENO, Ofir, A.; 148 Poli Street, Ventura, CA 93001 (US).		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: BICYCLIC PYRIDINE AND PYRIMIDINE DERIVATIVES AS NEUROPEPTIDE Y RECEPTOR ANTAGONISTS			
(57) Abstract			
There are provided compounds, compositions and methods of use thereof in the modulation of feeding behavior, obesity, diabetes, cancer (tumor), inflammatory disorders, depression, stress related disorders, Alzheimer's disease and other disease conditions.			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

BICYCLIC PYRIDINE AND PYRIMIDINE DERIVATIVES AS NEUROPEPTIDE Y RECEPTOR ANTAGONISTS

This patent application claims priority to U.S.
5 provisional patent applications serial nos. 60/073,927
(filed on February 6, 1998); 60/073,981 (filed on
February 6, 1998); 60/093,482 (filed on July 20, 1998);
and 60/093,577 (filed on July 20, 1998), each of which
is incorporated herein by reference in its entirety.

10

Background of the Invention

Neuropeptide Y ("NPY") is a 36 amino acid peptide
related to and a member of the "PP" peptide family
which includes peptide YY ("PYY") and pancreatic
15 peptide ("PP") (See, Tatemoto, et al. Nature, 296, 659
(1982); Tatemoto, Proc. Natl. Acad. Sci USA, 79, 5485
(1982)). NPY is named for the presence of an
N-terminal tyrosine and a C-terminal tyrosine amide and
is the most abundant peptide neurotransmitter in the
20 brain and central nervous system. NPY is found also in
various parts of the peripheral nervous system. This
peptide mediates several important biological
activities through various receptors and receptor
subtypes as discussed below.

25 In the brain, high NPY levels are found in the
cerebral cortex, hippocampus, thalamus, hypothalamus
and brainstem. Dense NPY staining occurs in the
hypothalamic, brainstem and some limbic regions
suggesting that NPY plays a role in somatic, sensory or
30 cognitive brain function. Studies have suggested, also
that NPY plays a role in the regulation of food intake,
particularly in eating disorders including, for
example, obesity, anorexia and bulimia, and memory
retention and other cognitive functions, as well as
35 anxiolysis and depression.

Additionally, NPY is found in both peripheral nerves and in the circulation. NPY appears to be a co-transmitter with norepinephrine, playing a role in vasoconstriction and hypertension, cardiac
5 contractility, analgesia and hyperalgesia, as well as control of secretory activity in the intestine.

As noted, NPY and NPY analogs, mediate the noted biological functions through a family of closely related receptor and receptor subtypes. Presently,
10 five receptor subtypes have been identified and are designated Y1 through Y5. Each receptor subtype generally is associated with different biological activities.

For example, the Y1 receptor is believed to be
15 responsible for mediating many of the central and peripheral activities of NPY, including the anxiolytic and sedative effects, as well as the observed vasoconstrictive activities.

The Y2 receptor is predominant in the brain,
20 particularly in the hippocampus. The Y2 receptor mediated effects are associated with inhibition of adenylate cyclase and inhibition of transmitter release. The Y2 receptor effects include vasoconstriction in some blood vessels, antisecretory
25 effects in the intestine, enhanced memory retention, and inhibition of lipolysis.

The Y3 receptor effects are associated with inhibition of adenylate cyclase and elevation of intracellular calcium ion concentrations. Biological
30 effects observed for Y3 include hypotension and bradycardia, inhibition of cardiac contractile force, inhibition of glutamate responsiveness and baroreceptor reflex, inhibition of catecholamine release and release of aldosterone.

35 The Y4 receptor(also referred to as "PP1" receptor) may be involved in pancreatic exocrine

secretion and hormonal control and may be important in diabetes or conditions associated with diabetes.

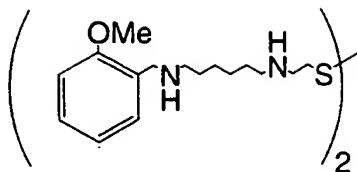
The most recently identified receptor is Y5 (sometimes referred to as "Y1-like" or "Feeding" receptor) (See, Gerald et al., Nature, 382, 168 (1996) and Hu et al., J. Biol. Chem., 271, 26315 (1996)). This receptor is associated with food intake and may mediate eating disorders such as obesity, bulimia and anorexia. Recently, Y5 has been implicated in the mediation of epileptic states and thus, NPY may be an endogenous anticonvulsant agent (See, e.g. Woldbye et al. Nat. Med., 3, 761 (1997)).

For several articles describing NPY, NPY analogs and receptors, see, for example, Hipskind, P. and Gehler, D., "Annual Reports in Medicinal Chemistry," 31, pp. 1-10, Robertson ed., (1996); Grunemar, L. and Håkanson, R., "TiPS Reviews," Vol. 15, p. 153, Elsevier Science Ltd. (1994); Munglani, R. et al., "Drugs," 52(3), 371 (1996); and Balasubramaniam, A., "Peptides", 18(3), 445 (1997), and references cited therein.

Because of the biological importance of NPY and the receptors with which it interacts, researchers have sought mediators, particularly antagonists, as novel therapeutic agents. A variety of peptide derivatives and analogs have been prepared in which amino acid modifications, substitutions, and deletions have been made relative to NPY. See, e.g., Hipskind, supra.

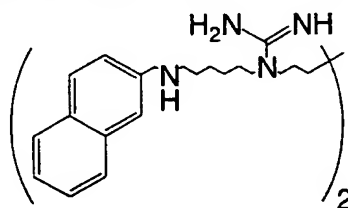
Although it would be preferable to have an easily synthesized, physically and metabolically stable and perhaps orally active NPY modulating compound, only a few non-peptide antagonists have been prepared. For example, a few non-peptidyl antagonists include the following:

4



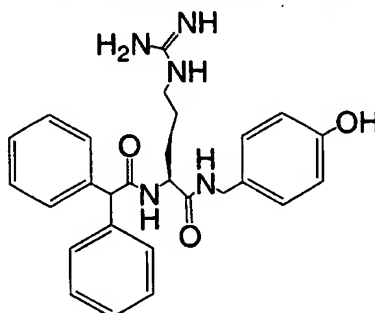
Benextramine

See Doughty, M. B. *et al.*, *Eur. J. Pharmacol.*, **185**, 113 (1990); *J. Pharmacol. Exp. Ther.*, **265**, 172 (1993);



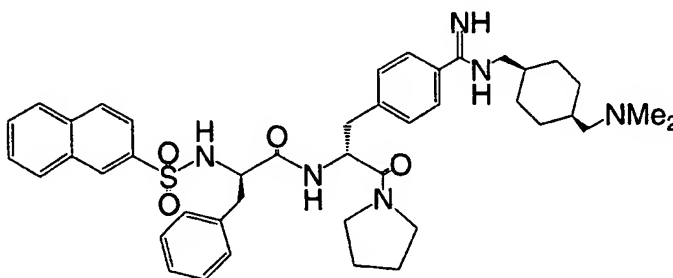
CC2137

See, Chaurasia, C., *J. Med. Chem.*, **37**, 2242 (1994);



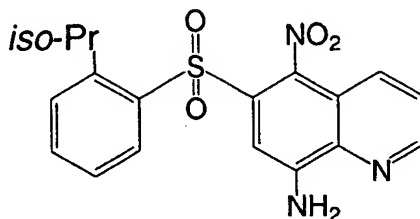
BIBP3226

10 See, Rudolf, K., *et al.*, *Eur. J. Pharmacol.*, **271**, R11-R13 (1994); Sautel, M., *et al.*, *Mol. Pharmacol.*, **50**, 285 (1996);



SR120819A

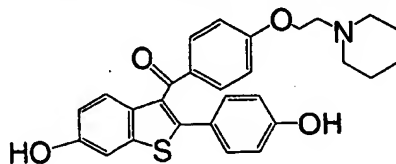
See, Serradeil-Le Gal, C., et al., FEBS Lett., 362, 192 (1995); Serradeil-Le Gal, C., et al., Soc. Neurosci. Abstr. 376.14 (1994);



5

PD160170

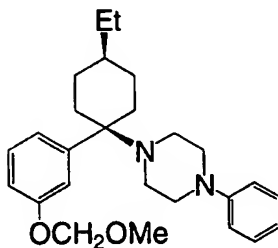
See, Wright, J. L., et al., Bioorg. Med. Chem. Lett.,
6, 1809 (1996); Wright, J. L., et al., 211th ACS
National Meeting, New Orleans, Louisiana (1996);



10

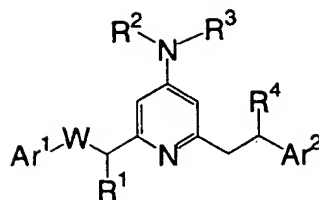
raloxifene

See, for example, Bruns, R. et al., PCT publications, WO 96/12489 and 96/12490; U.S. Pat. No. 5,504,094 (Apr. 2, 1996); and,

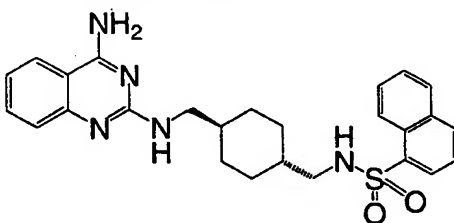


15 See Peterson, J. M., et al., PCT Publication
WO 96/14307.

Additionally, compounds of the following general structure, described in PCT publication, WO 97/34873 (published Sept. 25, 1997), are noted to be useful in the treatment of hyperphagia, obesity or diabetes:



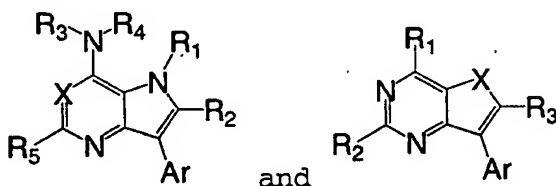
Further, the following compound and related compounds are noted to be useful in NPY5 associated disorders and are disclosed in PCT publications,
 5 WO 97/20823, WO 97/20820, WO 97/20821. and WO 97/20822:



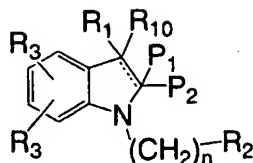
and WO 98/35944 and WO 98/35957 disclose substituted alkylamide NPY5 receptor antagonists.

See, also, L. Criscione, et al., Society for
 10 Neuroscience, 23, Abstract No. 231.2, (1997).

Other published compounds include the following general formulae:



15 (See, respectively, PCT publication, WO 96/35689, published Nov. 14, 1996 - CRF1 receptor agonist or antagonist compounds useful for treating and diagnosis of stress related disorders; and PCT publication, WO 97/29110, published Aug. 14, 1997 - CRF receptor
 20 antagonist compounds useful for treating disorders relating to hypersecretion of CRF); and,



(See, PCT Publication, WO 95/33748, published Dec. 14, 1995 - endothelin receptor antagonists).

Obesity, defined as an excess of body fat relative to lean body mass, is associated with important psychological and medical morbidities, the latter including hypertension, elevated blood lipids, and Type II or non-insulin dependent diabetes mellitus ("NIDDM"). There are over 6 million individuals with NIDDM in the United States, including approximately 20% of the population 65 years or older. See, Harris *et al.*, *Int. J. Obes.*, **11**, 275 (1987). Approximately 45% of males and 70% of females with NIDDM are obese, and their diabetes is substantially improved or eliminated by weight reduction. See, Harris, *Diabetes Care*, **14**(3), 639 (1991).

The assimilation, storage and utilization of nutrient energy is a complex system central to survival of a warm-blooded animal. Among land-dwelling mammals, storage in adipose tissue of large quantities of metabolic fuel as triglycerides is crucial for surviving through periods of food deprivation. The need to maintain a fixed level of energy stores without continual alteration in the size and shape of an organism requires the achievement of a balance between energy intake and expenditure.

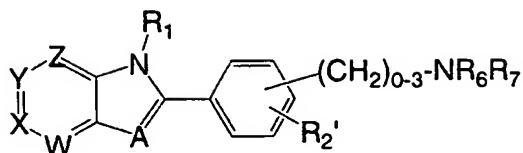
Models of obesity which use animals with mutations in the *ob* and *db* gene indicate that the animals have an altered metabolism of carbohydrates resembling Type II diabetes in humans. These animals show effects which resemble other aspects of obesity. In particular, mice with these mutations eat more food and expend less energy than lean control animals. The phenotype is

similar to that observed in animals with lesions of the ventromedial hypothalamus which indicates that the noted mutations may interfere with the ability to properly integrate or respond to nutritional
5 information within the central nervous system. See, for example, Coleman, Diabetologia, 2, 294 (1973)

These studies and others related to NPY and NPY receptors show that there is an interaction of a variety of mechanisms involved in the development and
10 maintenance of obesity, overeating and apparently related disease states such as diabetes, or even other NPY mediated disease states such as anxiety and depression. These may include a variety of genetic factors including modifications in the ob, db and NPY
15 genes or receptors, or gene products which affect or modulate these receptors or gene products, including control mechanisms of these receptors or gene products, or control mechanisms of other receptors or targets either upstream or downstream in the signaling pathway
20 from the noted genes, receptors or other target molecules.

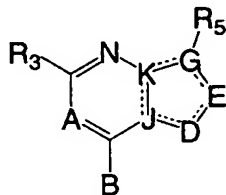
Given the variety of clinical states associated with eating disorders, including hyperphagia, obesity, diabetes, and other disease states related to the
25 various mechanisms involved including, for example, NPY pathways, a need exists for additional compounds capable of modulating such activities. In particular, there is a need to provide new approaches for the treatment or prophylaxis of obesity, overeating and
30 diabetes and other diseases which are mediated by the same or related pathways associated with these diseases.

WO 98/06703 (incorporated herein in its entirety) discloses that compounds of the general formula



wherein A, W, X, Y, Z, R₁, R₂', R₆ and R₇ are as defined therein, are monocyte chemoattractant protein 1 (MCP-1) receptor antagonists and are capable of inhibiting the binding of MCP-1 to its receptor. MCP-1, a chemokine (chemoattractant cytokine), appears to be involved in inflammation by acting on monocytes, activated memory T cells and on basophils. MCP-1 is a potent secretagogue of inflammatory mediators for monocytes and basophils and appears to have chemotactic activity for human monocytes and/or T cells. MCP-1 may also play a role in allergic hypersensitivity disease. Further, MCP-1 selectively activates the B1 integrin family of leukocyte adhesion molecule and may play a role in leukocyte interactions with the extracellular matrix. Thus, MCP-1 may not only trigger the initial arrest and adhesion of monocytes and T cells, but may also act to guide their migration in extravascular space.

WO 98/08847 (incorporated herein by reference in its entirety) discloses that compounds of the general formula

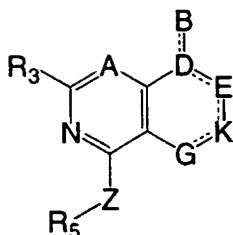


wherein R₃, R₅, A, B, D, E, G, J and K are as defined therein, are corticotropin releasing factor (CRF) antagonists, corticotropin releasing factor hormone (CRH) binding protein inhibitors and are also useful in the treatment of inflammatory disorders. The CRF antagonists were reported to be effective in the treatment of stress-related illnesses, mood disorders

such as depression, major depressive disorder, single episode depression, recurrent depression, child abuse induced depression, postpartum depression, dysthymia, bipolar disorders and cyclothymia; chronic fatigue syndrome; eating disorders such as anorexia and bulimia nervosa; generalized anxiety disorder; panic disorder; phobias; obsessive-compulsive disorder, post-traumatic stress disorder, pain perception such as fibromyalgia; headache; gastrointestinal diseases; hemorrhagic stress; ulcers; stress-induced psychotic episodes; fever; diarrhea; post-operative ileus, colonic hypersensitivity; irritable bowel syndrome; Crohn's disease; spastic colon; inflammatory disorders such as rheumatoid arthritis and osteoarthritis; pain; asthma; psoriasis; allergies; osteoporosis; premature birth; hypertension, congestive heart failure; sleep disorders; neurodegenerative diseases such as Alzheimer's disease, senile dementia of the Alzheimer's type, multiinfarct dementia, Parkinson's disease, and Huntington's disease; head trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; spinal cord trauma; psychosocial dwarfism; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone; obesity; chemical dependencies and addictions; drug and alcohol withdrawal symptoms; cancer; infertility; muscular spasms; urinary incontinence; hypoglycemia and immune dysfunctions including stress induced immune dysfunctions, immune suppression and human immunodeficiency virus infections; and stress-induced infections in humans and animals. CRH binding protein inhibitors were reported to be effective in the treatment of Alzheimer's disease and obesity.

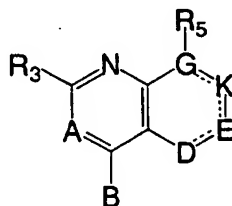
WO 98/05661 (incorporated herein by reference in its entirety) discloses that compounds of the general formula

11



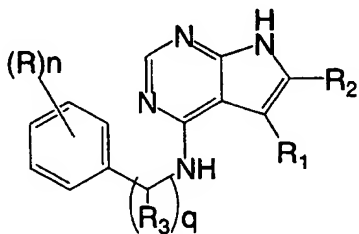
wherein R_3 , R_5 , A, B, D, E, G, K and Z are as defined therein, are CRF antagonists, CRH binding protein inhibitors and are also useful in the treatment of inflammatory disorders.

WO 98/08846 (incorporated herein by reference in its entirety) discloses that compounds of the general formula



wherein R_3 , R_5 , A, B, D, E, G and K are as defined therein, are CRF antagonists, CRH binding protein inhibitors and are also useful in the treatment of inflammatory disorders.

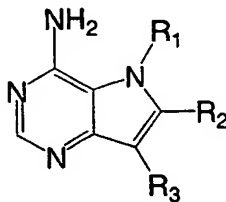
WO 98/07726 (incorporated herein by reference in its entirety) discloses that compounds of the general formula



wherein R , R_1 , R_2 , R_3 , n and q are as defined therein, are protein tyrosine kinase inhibitors and/or inhibitors of protein serine/threonine kinases. The compounds were reported to inhibit the tyrosine kinase activity of the receptor for the epidermal growth

factor (EGF) and of c-erbB2 kinase. These receptor-specific enzyme activities play a key role in signal transmission in a large number of mammalian cells, including human cells, especially epithelial cells, cells of the immune system and cells of the central and peripheral nervous system. In various cell types, EGF-induced activation of receptor-associated protein tyrosine kinase (EGF-R-PTK) is a prerequisite for cell division and thus for the proliferation of the cell population. Inhibition of protein kinases, such as EGF-receptor-specific tyrosine kinase, inhibits the proliferation of the cells. The compounds were also reported to inhibit other protein tyrosine kinases that are involved in signal transmission mediated by trophic factors, for example abl kinase (such as v-abl kinase), kinases from the family of the src kinases (such as c-src kinase), lck, fyn, other kinases of the EGF family (such as c-erbB2 kinase (HER-2), c-erbB3 kinase, c-erbB4 kinase), members of the family of the PDGF receptor protein tyrosine kinases (such as PDGF receptor kinase, CSF-1 receptor kinase, Kit receptor kinase, VEGF receptor kinase and FGF receptor kinase), the receptor kinase of the insulin-like growth factor (IGF-1 kinase), and serine/threonine kinases (such as protein kinase C or cdc kinases), all of which play a part in growth regulation and transformation in mammalian cells, including human cells.

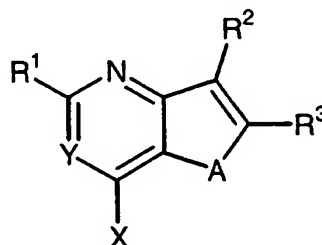
WO 97/49706 (incorporated herein by reference in its entirety) discloses that compounds of the general formula



wherein R_1 , R_2 , and R_3 are as defined therein, are protein tyrosine kinase inhibitors.

Summary of the Invention

5 There is a need to provide therapeutic and prophylactic methods for the modulation of feeding behavior, obesity, diabetes, cancer (tumor), inflammatory disorders, depression, stress related disorders, Alzheimer's disease and other disease
10 conditions. Additionally, there is a need to provide therapeutic and prophylactic methods for the modulation of other disease states which result from the same or related biological pathways, including the biological pathways which are mediated by NPY and/or NPY
15 receptors; CRF and/or CRH binding protein; protein tyrosine kinases and/or of protein serine/threonine kinases; MCP-1 and/or its receptor; and the like. The present invention provides compounds which can be used to modulate such activities. In particular, the present
20 invention provides novel compounds and methods for modulating feeding behavior, obesity or diabetic conditions, as well as other disease states associated with the same pathways effecting the noted disease states, especially those modulated by NPY or NPY
25 receptors and related pathways. Compounds useful in the various aspects of the invention are represented by the formula



wherein A , X , Y , R^1 , R^2 and R^3 are defined below.

30 Additionally, there are provided formulations which comprise a compound of this invention in

combination with a pharmaceutically acceptable carrier, diluent or excipient therefor. These formulations may be used in the noted methods. Further, there are provided processes for preparing the compounds of this invention.

Brief Description of the Drawings

Fig. 1 outlines a general reaction scheme for the synthesis of pyrrolo[3,2-d]pyrimidines of the invention.

Fig. 2 outlines a general reaction scheme for the synthesis of pyrrolo[3,2-d]pyridines and pyrrolo[3,2-d]pyrimidines.

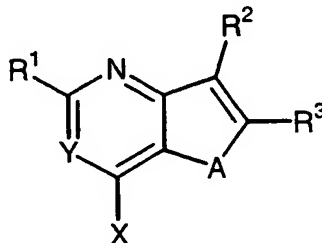
Fig. 3 provides a general process for the synthesis of thiopheno-, furano-, and pyrrolo-[3,2-d]-pyrimidines and -pyridines of the invention.

Fig. 4 provides a general process for the synthesis of 5-hydrocyclopenta[2,1-d]pyrimidines of the invention.

In the drawings, L represents a leaving group familiar to one skilled in the art and E represents $-\text{CO}_2\text{CH}_3$, $-\text{C}(\text{O})\text{X}$ or $-\text{CN}$, wherein X is a halogen.

Detailed Description of the Invention

In accordance with the present invention, there is provided compounds of the formula:



or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or C(R⁶);

A is O, S, S(O), S(O)₂, N-H, N-R⁴ or CR⁴R⁷; preferably, A is O, S, S(O)₂, N-H, N-R⁴ or CHR⁴; more preferably, A is O, S, N-H or N-R⁴; more preferably, A is O, S or N-H; most preferably, A is N-H;

5

R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, -Z(aryl), -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl or -Z(Q) radical; preferably, R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, aryl, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl or -Z(Q) radical; more preferably, R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, aryl, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl or -Z(Q) radical; more preferably, R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl radical; more preferably, R⁶ is a hydrogen, -OH, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl), -N((C₁-C₂)alkyl)₂, or (C₁-C₄)alkyl radical; more preferably, R⁶ is a hydrogen, -OH, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₂)alkoxy or (C₁-C₂)alkyl radical; most preferably, R⁶ is a hydrogen radical;

25

R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical; preferably, R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),

35

- Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical; more preferably, R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl),
- 5 -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical; more preferably, R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₆)cycloalkyl,
- 10 -Z((C₁-C₈)alkoxy), -Z((C₃-C₆)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(N(R⁵)₂) or -Z(Q) radical; more preferably, R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-cyclopropyl or -(NR¹⁰)_k((C₁-C₂)alkyl)_k-N(R¹⁰)₂ radical;
- 15 more preferably, R¹ is a bromo, chloro, fluoro, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₂)alkyl, (C₁-C₂)alkoxy, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-cyclopropyl, -NH₂ or -NH((C₁-C₂)alkyl) radical; most preferably, R¹ is a -CF₃, -OCF₃, methyl, methoxy, cyclopropyl, -NH₂ or -NH-methyl
- 20 radical; alternatively, preferably, R¹ is not an optionally substituted aryl or heteroaryl radical;
- X is a hydrogen, halo, -OH, -NO₂, -NHOH, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy),
- 25 -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical; preferably, X is a (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl,
- 30 -(NR⁵)_k((C₁-C₈)alkyl)(C₁-C₈)alkoxy, -(NR⁵)_k((C₁-C₈)alkyl)aryloxy, -(NR⁵)_k((C₁-C₈)alkyl)_kS(O)_pR⁵, -(NR⁵)_k((C₁-C₈)alkyl)S(O)_pR⁵, -(NR⁵)D(C₁-C₈)alkoxy, -(NR⁵)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy, -(NR⁵)_k(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
- 35 -(NR⁵)_k(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy, -(NR⁵)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_maryloxy,

- $-(NR^5)_x(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_x(CH_2)_n\text{aryloxy}$,
 $-(NR^5)_x(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_n\text{aryloxy}$, $-Z(S(O)_qR^5)$,
 $-Z(\text{aryl})$, $-Z(\text{heteroaryl})$, $-Z((C_3-C_{10})\text{cycloalkyl})$,
 $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$,
5 $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$ or
 $-Z(Q)$ radical; more preferably, X is a
 $-(NR^5)_x((C_1-C_8)\text{alkyl})(C_1-C_8)\text{alkoxy}$,
 $-(NR^5)_x((C_1-C_8)\text{alkyl})\text{aryloxy}$, $-(NR^5)_x((C_1-C_8)\text{alkyl})_xS(O)_pR^5$,
 $-(NR^5)_x((C_1-C_8)\text{alkyl})S(O)_pR^5$, $-(NR^5)D(C_1-C_8)\text{alkoxy}$,
10 $-(NR^5)(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_x(CH_2)_n(C_1-C_8)\text{alkoxy}$,
 $-(NR^5)_x(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_x(CH_2)_n(C_1-C_8)\text{alkoxy}$,
 $-(NR^5)_x(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_n(C_1-C_8)\text{alkoxy}$,
 $-(NR^5)(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_x(CH_2)_n\text{aryloxy}$,
 $-(NR^5)_x(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_x(CH_2)_n\text{aryloxy}$,
15 $-(NR^5)_x(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_n\text{aryloxy}$, $-Z(S(O)_qR^5)$,
 $-Z(\text{aryl})$, $-Z(\text{heteroaryl})$, $-Z((C_3-C_{10})\text{cycloalkyl})$,
 $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$,
 $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$ or
 $-Z(Q)$ radical; more preferably, X is a
20 $-(NR^{10})((C_1-C_8)\text{alkyl})(C_1-C_8)\text{alkoxy}$,
 $-(NR^{10})((C_1-C_8)\text{alkyl})\text{aryloxy}$, $-(NR^{10})S(O)_pR^5$,
 $-(NR^{10})((C_1-C_8)\text{alkyl})S(O)_pR^5$, $-(NR^{10})D(C_1-C_8)\text{alkoxy}$,
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_x(CH_2)_n(C_1-C_8)\text{alkoxy}$,
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_x(CH_2)_n(C_1-C_8)\text{alkoxy}$,
25 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_n(C_1-C_8)\text{alkoxy}$,
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_x(CH_2)_n\text{aryloxy}$,
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_x(CH_2)_n\text{aryloxy}$,
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_n\text{aryloxy}$,
 $-(NR^{10})D(S(O)_qR^5)$, $-(NR^{10})D'(S(O)_qR^5)$, $-(NR^{10})D(\text{aryl})$,
30 $-(NR^{10})D'(\text{aryl})$, $-(NR^{10})D(\text{heteroaryl})$,
 $-(NR^{10})D'(\text{heteroaryl})$, $-(NR^{10})D((C_3-C_{10})\text{cycloalkyl})$,
 $-(NR^{10})D'((C_3-C_{10})\text{cycloalkyl})$, $-(NR^{10})D(NR^{10}SO_2R^5)$,
 $-(NR^{10})D'(NR^{10}SO_2R^5)$, $-(NR^{10})D(CON(R^5)_2)$, $-(NR^{10})D'(CON(R^5)_2)$,
 $-(NR^{10})D(CO_2R^5)$, $-(NR^{10})D'(CO_2R^5)$, $-(NR^{10})D(N(R^5)_2)$, $-N(R^5)_2$,
35 $-(NR^{10})D'(N(R^5)_2)$, $-(NR^{10})D(NR^{10}CON(R^5)_2)$,
 $-(NR^{10})D'(NR^{10}CON(R^5)_2)$, $-(NR^{10})D(NR^{10}(CO)R^5)$,

- $-(NR^{10})D'(NR^{10}(CO)R^5)$, $-(NR^{10})D(NR^{10}CO_2R^5)$,
 $-(NR^{10})D'(NR^{10}CO_2R^5)$, $-(NR^{10})D(COR^5)$, $-(NR^{10})D'(COR^5)$,
 $-(NR^{10})D-Q$, $-(NR^{10})D'-Q$ or Q radical; more preferably, X
 is a $-(N((C_1-C_4)alkyl))-(C_1-C_4)alkyl)aryloxy$,
 5 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_x(CH_2)(C_1-C_4)alkoxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_x(CH_2)_m(C_1-C_4)alkoxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$,
 10 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_x(CH_2)aryloxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_x(CH_2)_maryloxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_maryloxy$,
 $-(N((C_1-C_4)alkyl))-D(aryl)$, $-(N((C_1-C_4)alkyl))-D'(aryl)$,
 15 $-(N((C_1-C_4)alkyl))-D(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D'(heteroaryl)$,
 $-(N((C_1-C_4)alkyl))-D(NR^{10}SO_2R^5)$,
 $-(N((C_1-C_4)alkyl))-D(CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(CO_2R^5)$,
 $-(N((C_1-C_4)alkyl))-D(N(R^5)_2)$, $-N(R^5)_2$,
 $-(N((C_1-C_4)alkyl))-D(NR^{10}CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}(CO)R^5)$,
 20 $-(N((C_1-C_4)alkyl))-D(NR^{10}CO_2R^5)$,
 $-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))-D-Q$,
 $-(N((C_1-C_4)alkyl))-D'-Q$ or Q radical; more preferably, X
 is a $-N((C_1-C_4)alkyl)_2$ or 4-membered to 10-membered
 heterocyclyl or heteroaryl ring, having a nitrogen atom
 25 ring member bonded directly to the carbon atom
 adjoining X , optionally substituted with 1-2 radicals
 of R^8 ; most preferably, 5-membered to 6-membered
 heterocyclyl ring, having a nitrogen atom ring member
 bonded directly to the carbon atom adjoining X and
 30 containing an additional 0-1 nitrogen, oxygen or sulfur
 atom ring member, which is optionally substituted with
 1-2 radicals of R^8 ;

wherein each R^{10} is independently a hydrogen or
 35 $(C_1-C_4)alkyl$ radical; preferably, wherein each R^{10} is
 independently a hydrogen or $(C_1-C_2)alkyl$ radical;

- alternatively, X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic carbocyclic or
- 5 heterocyclic ring which is optionally substituted with 1-2 radicals of R^8 ; preferably, X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic
- 10 heterocyclic ring which is optionally substituted with 1-2 radicals of R^8 ; more preferably, X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic
- 15 heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8 ; more preferably, X and A, when A is N or C, together with the adjoining carbon atoms form a 8-membered to 10-membered bicyclic heterocyclyl
- 20 moiety which is optionally substituted with 1-2 radicals of R^8 ; most preferably, X and A, when A is N or C, together with the adjoining carbon atoms form a 8-membered to 10-membered bicyclic heterocyclyl moiety containing 1-2 nitrogen atom and 0-1 oxygen or sulfur atom ring members and which is optionally substituted with 1-2 radicals of R^8 on ring carbon atoms;
- 25 R^2 is a hydrogen, halo, -OH, -NO₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵),
- 30 -Z(S(O)_pR⁵) or -Z(Q); preferably, R^2 is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂),
- 35 -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical; more preferably, R^2 is a

- hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂),
- 5 -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(S(O)_pR⁵) or -Z(Q) radical; more preferably, R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR¹⁰SO₂R⁵),
- 10 -Z(CON(R⁵)₂), -Z(N(R⁵)₂), -Z(NR¹⁰CON(R⁵)₂), -Z(NR¹⁰(CO)R⁵), -Z(NR¹⁰CO₂R⁵), -Z(S(O)_pR⁵) or -Z(Q) radical; more preferably, R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, - (NR¹⁰)_k((C₁-C₂)alkyl)_k-(C₁-C₄)alkoxy),
- 15 - (NR¹⁰)_k((C₁-C₂)alkyl)_k-(CON(R⁵)₂), - (NR¹⁰)_k((C₁-C₂)alkyl)_k-(N(R⁵)₂), - (NR¹⁰)_k((C₁-C₂)alkyl)_k-(S(O)_pR⁵) or - (NR¹⁰)_k((C₁-C₂)alkyl)_k-Q radical; more preferably, R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₂)alkyl or (C₁-C₂)alkoxy radical; most preferably, R² is a
- 20 hydrogen, -CF₃ or methyl radical;

- R³ is a hydrogen, halo, -OH, -NO₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl),
- 25 -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q); preferably, R³ is a (C₃-C₁₀)cycloalkyl, (C₁-C₈)alkyl, -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-, -((C₁-C₈)alkyl)N(R⁵)₂,
- 30 -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl), -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH, -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
- 35 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy, -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,

- $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_nN(R^5)_2,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_nN(R^5)_2,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)N(R^5)_2,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_pS(O)_qR^5, -D'(S(O)_qR^5),$
5 $-D'(\text{aryloxy}), -D'(\text{aryl}), -D'(\text{heteroaryl}),$
 $-D'((C_3-C_{10})\text{cycloalkyl}), -D'(NR^5SO_2R^5), -D'(CON(R^5)_2),$
 $-D'(CO_2R^5), -D'(NR^5CON(R^5)_2), -D'(NR^5(CO)R^5), -D'(NR^5CO_2R^5),$
 $-D'(COR^5), -D'(Q), -D(\text{aryloxy}), -D(\text{aryl}),$
 $-D(\text{heteroaryl}), -D((C_3-C_{10})\text{cycloalkyl}), -D(NR^5SO_2R^5),$
10 $-D(CON(R^5)_2), -D(CO_2R^5), -D(S(O)_qR^5), -D(NR^5CON(R^5)_2),$
 $-D(NR^5(CO)R^5), -D(NR^5CO_2R^5), -D(COR^5) \text{ or } -(NR^5)_k-D-Q$
radical; more preferably, R^3 is a $(C_3-C_{10})\text{cycloalkyl},$
 $(C_3-C_8)\text{alkyl}, -((C_1-C_8)\text{alkyl})OH, (C_1-C_8)\text{alkoxy-}$
 $(C_1-C_8)\text{alkyl-}, -((C_1-C_8)\text{alkyl})N(R^5)_2,$
15 $-((C_1-C_8)\text{alkyl})S(O)_p((C_1-C_8)\text{alkyl}),$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_nOH,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_nOH,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)OH,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_m(C_1-C_8)\text{alkoxy},$
20 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_m(C_1-C_8)\text{alkoxy},$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)(C_1-C_8)\text{alkoxy},$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_nN(R^5)_2,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_nN(R^5)_2,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)N(R^5)_2,$
25 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_pS(O)_qR^5,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_m(CO_2R^5),$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_m(COR^5),$
 $-((C_1-C_8)\text{alkyl})(CO_2R^5), -((C_1-C_8)\text{alkyl})(COR^5),$
 $-D'(S(O)_qR^5), -D'(\text{aryloxy}), -D'(\text{aryl}), -D'(\text{heteroaryl}),$
30 $-D'((C_3-C_{10})\text{cycloalkyl}), -D'(NR^5SO_2R^5), -D'(CON(R^5)_2),$
 $-D'(NR^5CON(R^5)_2), -D'(NR^5(CO)R^5), -D'(NR^5CO_2R^5), -D'(Q),$
 $-D(\text{aryloxy}), -D(\text{aryl}), -D(\text{heteroaryl}),$
 $-D((C_3-C_{10})\text{cycloalkyl}), -D(NR^5SO_2R^5), -D(CON(R^5)_2),$
 $-D(S(O)_qR^5), -D(NR^5CON(R^5)_2), -D(NR^5(CO)R^5), -D(NR^5CO_2R^5) \text{ or}$
35 $-(NR^5)_k-D-Q$ radical; more preferably, R^3 is a
 $(C_3-C_{10})\text{cycloalkyl}, (C_3-C_8)\text{alkyl}, -((C_1-C_8)\text{alkyl})OH,$

- (C_1-C_8) alkoxy- (C_1-C_8) alkyl-, $-((C_1-C_8)$ alkyl) $N(R^5)_2$,
 $-((C_1-C_8)$ alkyl) $S(O)_p((C_1-C_8)$ alkyl),
 $-(CH_2)((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_mOH$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_mOH$,
5 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_mOH$,
 $-(CH_2)((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(CH_2)((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
10 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_mS(O)_pR^5$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(CO_2R^5)$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(COR^5)$,
15 $-((C_1-C_8)$ alkyl) (CO_2R^5) , $-((C_1-C_8)$ alkyl) (COR^5) ,
 $-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$,
 $-D'((C_3-C_{10})$ cycloalkyl), $-D'(NR^{10}SO_2R^5)$, $-D'(CON(R^5)_2)$,
 $-D'(NR^{10}CON(R^5)_2)$, $-D'(NR^{10}(CO)R^5)$, $-D'(NR^{10}CO_2R^5)$, $-D'(Q)$,
 $-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$,
20 $-D((C_3-C_{10})$ cycloalkyl), $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$,
 $-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$
or $-(NR^{10})_k-D-Q$ radical; more preferably, R^3 is a
 (C_3-C_6) cycloalkyl, (C_3-C_6) alkyl, $-((C_1-C_4)$ alkyl) OH ,
 (C_1-C_4) alkoxy- (C_1-C_4) alkyl-, $-((C_1-C_4)$ alkyl) $N(R^5)_2$,
25 $-(CH_2)((C_3-C_6)$ cycloalkyl) $_k(CH_2)_mOH$,
 $-(CH_2)_m((C_3-C_6)$ cycloalkyl) $(CH_2)_mOH$,
 $-(CH_2)_m((C_3-C_6)$ cycloalkyl) $_k(CH_2)_mOH$,
 $-(CH_2)((C_3-C_6)$ cycloalkyl) $_k(CH_2)_m(C_1-C_4)$ alkoxy,
 $-(CH_2)_m((C_3-C_6)$ cycloalkyl) $(CH_2)_m(C_1-C_4)$ alkoxy,
30 $-(CH_2)_m((C_3-C_6)$ cycloalkyl) $_k(CH_2)_m(C_1-C_4)$ alkoxy,
 $-(CH_2)((C_3-C_6)$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_6)$ cycloalkyl) $(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_6)$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_6)$ cycloalkyl) $(CH_2)_mS(O)_pR^5$,
35 $-(CH_2)_m((C_3-C_6)$ cycloalkyl) $(CH_2)_m(CO_2R^5)$,
 $-(CH_2)_m((C_3-C_6)$ cycloalkyl) $(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$,

- D' (aryloxy), -D' (aryl), -D' (heteroaryl),
 -D' ((C₃-C₁₀)cycloalkyl), -D' (Q), -D(aryloxy), -D(aryl),
 -D(heteroaryl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂), -D(S(O)_qR⁵),
 -D(NR¹⁰CON(R⁵)₂), -D(NR¹⁰(CO)R⁵), -D(NR¹⁰CO₂R⁵) or -(NR¹⁰)_k-D-
- 5 Q radical; more preferably, R³ is a (C₃-C₆)cycloalkyl,
 (C₃-C₆)alkyl, -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-
 (C₁-C₄)alkyl-, -((C₁-C₄)alkyl)N(R⁵)₂,
 -(CH₂)((C₅-C₆)cycloalkyl)_k(CH₂)_mOH,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mOH,
- 10 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)OH,
 -(CH₂)((C₅-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₂)alkoxy,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(C₁-C₂)alkoxy,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)(C₁-C₂)alkoxy,
 -(CH₂)((C₅-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂,
- 15 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)N(R⁵)₂,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mS(O)_pR⁵,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(CO₂R⁵),
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(COR⁵), -D'(S(O)_qR⁵),
- 20 -D' (aryloxy), -D' (aryl), -D' (heteroaryl),
 -D' ((C₃-C₆)cycloalkyl), -D' (Q), -D(aryloxy), -D(aryl),
 -D(heteroaryl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂), -D(S(O)_qR⁵),
 -D(NR¹⁰CON(R⁵)₂), -D(NR¹⁰(CO)R⁵), -D(NR¹⁰CO₂R⁵) or -(NR¹⁰)_k-D-
- 25 Q radical; more preferably, R³ is a (C₃-C₆)cycloalkyl,
 (C₃-C₆)alkyl, aryloxy-(C₁-C₂)alkyl-, aryl, heteroaryl,
 aryl-(C₁-C₂)alkyl-, heteroaryl-(C₁-C₂)alkyl- or
 (C₃-C₆)cycloalkyl-(C₁-C₂)alkyl- radical; and
 alternatively, preferably, R³ is not -SO₂NH₂;
- 30 R⁴ is a hydrogen, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl,
 -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl),
 -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵),
 -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂),
 -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q)
- 35 radical; preferably, R⁴ is a (C₁-C₈)alkyl,
 (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy),

-Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl),
 -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂),
 -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵),
 -Z(S(O)_pR⁵) or -Z(Q) radical; more preferably, R⁴ is a
 5 (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, -N(R⁵)₂ or -Z(Q) radical;
 more preferably, R⁴ is a (C₁-C₄)alkyl radical; most
 preferably, R⁴ is a methyl radical;

each R⁵ is independently a hydrogen, -OH, (C₁-C₈)alkoxy,
 10 aryl, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂,
 (C₁-C₈)alkyl or (C₃-C₁₀)cycloalkyl radical; preferably,
 each R⁵ is independently a hydrogen, -OH, (C₁-C₄)alkoxy,
 -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂, (C₁-C₄)alkyl or
 (C₃-C₆)cycloalkyl radical; more preferably, each R⁵ is
 15 independently a hydrogen, -OH, (C₁-C₄)alkoxy, -NH₂,
 -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂ or (C₁-C₄)alkyl
 radical; more preferably, each R⁵ is independently a
 hydrogen, -OH, (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl),
 -N((C₁-C₂)alkyl)₂ or (C₁-C₂)alkyl radical; most
 20 preferably, each R⁵ is independently a hydrogen, -OH,
 (C₁-C₂)alkoxy, -NH₂ or (C₁-C₂)alkyl radical;

R⁷ is a hydrogen, -OH, (C₁-C₈)alkoxy, aryl, -NH₂,
 -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl or
 25 (C₃-C₁₀)cycloalkyl radical; preferably, R⁷ is a hydrogen,
 -OH, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl),
 -N((C₁-C₄)alkyl)₂, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl
 radical; more preferably, R⁷ is a hydrogen, -OH,
 (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂,
 30 or (C₁-C₄)alkyl radical; more preferably, R⁷ is a
 hydrogen, -OH, -NH₂ or (C₁-C₂)alkyl radical; most
 preferably, R⁷ is a hydrogen or methyl radical;

Q is a 4-membered to 10-membered heterocyclyl or
 35 heteroaryl ring optionally substituted with 1-2
 radicals of R⁶; preferably, 4-membered to 7-membered

heterocyclyl or 5-membered, 6-membered, 9-membered or 10-membered heteroaryl ring, each of which is optionally substituted with 1-2 radicals of R^8 ;

- 5 each R^8 is independently a -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, or (C₁-C₈)alkyl radical; preferably, each R^8 is independently a -OH, halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂, or (C₁-C₄)alkyl
 10 radical; more preferably, each R^8 is independently a -OH, halo, -CF₃, -OCF₃, (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl), -N((C₁-C₂)alkyl)₂, or (C₁-C₂)alkyl radical; most preferably, each R^8 is independently a -OH, -CF₃ or methyl radical;

15

Z is D(NR⁵)_k, D'(NR⁵)_k, (NR⁵)_kD or (NR⁵)_kD'; preferably, Z is D(NR¹⁰)_k, D'(NR¹⁰)_k, (NR¹⁰)_kD or (NR¹⁰)_kD'; more preferably, Z is (NR¹⁰)_kD or (NR¹⁰)_kD';

- 20 D is -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m-; preferably, D is -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_m-; more preferably, -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_m-;

D' is -((C₁-C₈)alkyl)_k-; preferably, D' is

- 25 -((C₁-C₄)alkyl)_k-;

- each k is independently 0 or 1; each m is independently an integer between 0 and 6, preferably, between 0 and 4, more preferably, between 0 and 3, and most
 30 preferably between 0 and 2; each p is independently an integer between 0 and 2; and each q is independently 1 or 2; and

- wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R¹, R², R³, R⁴, R⁵,
 35 R⁶, R⁷ and R⁸ is optionally substituted with one or more

- radicals of halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{Z}(\text{COOH})$, $-\text{Z}(\text{OH})$,
 $-\text{Z}(\text{NO}_2)$, $-\text{Z}(\text{SH})$, $-(\text{C}_1-\text{C}_8)\text{alkyl}$, $-(\text{C}_1-\text{C}_8)\text{acyloxy}$,
 $-(\text{C}_3-\text{C}_{10})\text{cycloalkyl}$, $-\text{S}-((\text{C}_1-\text{C}_8)\text{alkyl})_k\text{-aryl}$,
 $-(\text{C}_1-\text{C}_8)\text{alkyl})_k\text{-SO}_2\text{NH-aryl}$, $-\text{S}-(\text{C}_1-\text{C}_8)\text{alkyl}$,
5 $-\text{Z}((\text{C}_1-\text{C}_8)\text{alkoxy})$, $-\text{Z}(\text{aryloxy})$, $-\text{Z}(\text{aryl})$,
 $-\text{Z}(\text{heteroaryl})$, $-\text{Z}((\text{C}_3-\text{C}_{10})\text{cycloalkyl})$, $-\text{Z}(\text{NR}^i\text{SO}_2\text{R}^j)$,
 $-\text{Z}(\text{CON}(\text{R}^i)_2)$, $-\text{Z}(\text{CO}_2\text{R}^i)$, $-\text{Z}(\text{N}(\text{R}^i)_2)$, $-\text{Z}(\text{NR}^i\text{CON}(\text{R}^i)_2)$,
 $-\text{Z}(\text{NR}^i(\text{CO})\text{R}^j)$, $-\text{Z}(\text{NR}^i\text{CO}_2\text{R}^j)$, $-\text{Z}(\text{COR}^i)$, $-\text{Z}(\text{S}(\text{O})_p\text{R}^i)$ or
 $-\text{Z}(\text{Q})$, wherein such aryl, heteroaryl, cycloalkyl and Q
10 substituents are optionally substituted with one or
more radicals of halo, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{N}(\text{R}^i)_2$,
 $-\text{C}(\text{O})\text{R}^i$, $-\text{CO}_2\text{R}^i$, $-\text{OR}^i$, $-\text{SR}^i$ or $(\text{C}_1-\text{C}_8)\text{alkyl}$; preferably,
each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or
aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7
15 is optionally substituted with 1-3 radicals of halo and
1-2 radicals of $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{Z}(\text{COOH})$, $-\text{Z}(\text{OH})$, $-\text{Z}(\text{NO}_2)$,
 $-\text{Z}(\text{SH})$, $-(\text{C}_1-\text{C}_8)\text{alkyl}$, $-(\text{C}_1-\text{C}_8)\text{acyloxy}$,
 $-(\text{C}_3-\text{C}_{10})\text{cycloalkyl}$, $-\text{S}-((\text{C}_1-\text{C}_8)\text{alkyl})_k\text{-aryl}$,
 $-(\text{C}_1-\text{C}_8)\text{alkyl})_k\text{-SO}_2\text{NH-aryl}$, $-\text{S}-(\text{C}_1-\text{C}_8)\text{alkyl}$,
20 $-\text{Z}((\text{C}_1-\text{C}_8)\text{alkoxy})$, $-\text{Z}(\text{aryloxy})$, $-\text{Z}(\text{aryl})$,
 $-\text{Z}(\text{heteroaryl})$, $-\text{Z}((\text{C}_3-\text{C}_{10})\text{cycloalkyl})$, $-\text{Z}(\text{NR}^i\text{SO}_2\text{R}^j)$,
 $-\text{Z}(\text{CON}(\text{R}^i)_2)$, $-\text{Z}(\text{CO}_2\text{R}^i)$, $-\text{Z}(\text{N}(\text{R}^i)_2)$, $-\text{Z}(\text{NR}^i\text{CON}(\text{R}^i)_2)$,
 $-\text{Z}(\text{NR}^i(\text{CO})\text{R}^j)$, $-\text{Z}(\text{NR}^i\text{CO}_2\text{R}^j)$, $-\text{Z}(\text{COR}^i)$, $-\text{Z}(\text{S}(\text{O})_p\text{R}^i)$ or
 $-\text{Z}(\text{Q})$, wherein such aryl, heteroaryl, cycloalkyl and Q
25 substituents are optionally substituted with 1-3
radicals of halo, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{N}(\text{R}^i)_2$, $-\text{C}(\text{O})\text{R}^i$,
 $-\text{CO}_2\text{R}^i$, $-\text{OR}^i$, $-\text{SR}^i$ or $(\text{C}_1-\text{C}_8)\text{alkyl}$; more preferably, each
alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or
aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7
30 is optionally substituted with 1-3 radicals of halo
and 1-2 radicals of $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^i$, $-\text{SR}^i$, $-\text{NO}_2$,
 $-(\text{C}_1-\text{C}_4)\text{alkyl}$, $-(\text{C}_1-\text{C}_4)\text{acyloxy}$, $-(\text{C}_3-\text{C}_6)\text{cycloalkyl}$,
 $-\text{S}-((\text{C}_1-\text{C}_4)\text{alkyl})_k\text{-aryl}$, $-(\text{C}_1-\text{C}_4)\text{alkyl})_k\text{-SO}_2\text{NH-aryl}$,
aryloxy, aryl, $-\text{NR}^i\text{SO}_2\text{R}^j$, $-\text{CON}(\text{R}^i)_2$, $-\text{CO}_2\text{R}^i$, $-\text{N}(\text{R}^i)_2$,
35 $-\text{NR}^i\text{CON}(\text{R}^i)_2$, $-\text{NR}^i(\text{CO})\text{R}^j$, $-\text{NR}^i\text{CO}_2\text{R}^j$, $-\text{COR}^i$,
 $-\text{S}(\text{O})_2(\text{C}_1-\text{C}_4)\text{alkyl}$ or Q, wherein such aryl, heteroaryl,

- cycloalkyl and Q substituents are optionally substituted with 1-2 radicals of halo, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{N}(\text{R}^9)_2$, $-\text{C}(\text{O})\text{R}^9$, $-\text{CO}_2\text{R}^9$, $-\text{OR}^9$, $-\text{SR}^9$ or $(\text{C}_1-\text{C}_4)\text{alkyl}$; more preferably, each alkyl, aryl, heteroaryl,
- 5 cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is optionally substituted with 1-2 radicals of halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{NO}_2$, $(\text{C}_1-\text{C}_4)\text{alkyl}$, $(\text{C}_1-\text{C}_4)\text{acyloxy}$, $-\text{NR}^9\text{SO}_2\text{R}^9$, $-\text{CON}(\text{R}^9)_2$, $-\text{CO}_2\text{R}^9$, $-\text{N}(\text{R}^9)_2$, $-\text{NR}^9\text{CON}(\text{R}^9)_2$, $-\text{NR}^9(\text{CO})\text{R}^9$, $-\text{NR}^9\text{CO}_2\text{R}^9$, $-\text{COR}^9$ or
- 10 $-\text{S}(\text{O})_2(\text{C}_1-\text{C}_4)\text{alkyl}$; more preferably, each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is optionally substituted with 1-2 radicals of halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^9$, $-\text{SR}^9$, $(\text{C}_1-\text{C}_2)\text{alkyl}$ or $-\text{N}(\text{R}^9)_2$; and
- 15 wherein each R^9 is independently a hydrogen or $(\text{C}_1-\text{C}_8)\text{alkyl}$ radical; preferably, each R^9 is independently a hydrogen or $(\text{C}_1-\text{C}_4)\text{alkyl}$ radical; more preferably, each R^9 is independently a hydrogen or
- 20 $(\text{C}_1-\text{C}_2)\text{alkyl}$ radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1 , R^2 and R^3 is 0-4, preferably, 0-3, more preferably 1-3;

25 most preferably, 1-2.

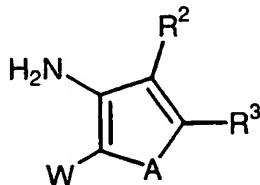
The following preferred provisos relate to compounds and pharmaceutical compositions of the invention:

- (a) when A is NH, Y is N, R^1 is H, methyl or phenyl,
- 30 and R^3 is methyl, ethyl or phenyl, then (1) when R^2 is H, X is not $-\text{NH}_2$, $-\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{NHCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_3)_2$, $-\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, $-\text{NHCH}_2\text{CH}_2\text{OH}$, $-\text{NH-phenyl}$, $-\text{NHCH}_2\text{CH}_2\text{-phenyl}$, $-\text{NH-CH}(\text{CH}_3)\text{CH}_2\text{-phenyl}$, $-\text{NH-(methoxyphenyl)}$, $-\text{NHCH}_2\text{CH}_2\text{-(dimethoxyphenyl)}$,
- 35 $-\text{NHCH}_2\text{CH}_2\text{-imidazolyl}$, $-\text{NHCH}_2\text{CH}_2\text{-(methylthioimidazolyl)}$, $-\text{NHCH}_2\text{CH}_2\text{-cyclohexyl}$, $-\text{NH-cyclohexyl}$, piperidinyl,

- morpholinyl, -NHNH₂, -NHCH(CH₃)₂, -NH-butyl, -NH-CH(CH₃)(CH₂)₄CH₃, -NH(CH₂)₂cyclohexenyl, -NH-(CH₂)₅CH₃, -NHCH₂CH=CH₂, -NH-CH₂-phenyl, 4-methylpiperazine, -NHSO₂(4-aminophenyl) or -NH-(4-methylpiperazine); (2)
- 5 when R² is -CH₂N(CH₂CH₃)₂, -CH₂NH-butyl, -CH₂NHCH₂CH₂-cyclohexenyl or -CH₂NHCH₂CH₂COOH, X is not -NH(CH₂)₂cyclohexenyl; and (3) when R₂ is methyl, acetyl or -COOCH₂CH₃, X is not -NH₂ or -NH(C(O)CH₃);
- (b) when R¹ is ethoxy, R² is H, R³ is -COOCH₂CH₃, A is NH
- 10 and Y is N, then X is not -NH₂;
- (c) when A is N-H or N-R⁴, Y is C-H and R¹ is hydrogen, halo, alkyl, cycloalkyl, alkoxy or alkylthio, then (1) when R³ is methyl and R² is acetyl or -COOCH₃, X is not NH₂ or trifluoromethylphenyl; (2) when R³ is methyl or
- 15 -COOCH₂CH₃ and R² is H, X is not methyl; and (3) when one of R², R³ or R⁴ is optionally substituted -ethyl-NR⁵CONHR⁵, X is not alkyl or cycloalkyl;
- (d) when A is N-R⁴ and Y is C-H, then R³ is not -CO₂R⁵;
- (e) when A is N-C₁-C₆ alkyl, Y is C-H or N, R¹ and R³ are
- 20 hydrogen, halo, alkyl, alkoxy or alkylthio, then R² is not thienyl optionally substituted with 1-3 halo, hydroxy, alkyl or alkoxy radicals;
- (f) when A is CH₂, Y is C-H, R¹ is NH₂, R³ is methyl and X is methyl, then R² is not C(O)NH₂;
- 25 (g) when A is N-H or N-R⁴ and R³ is aryl or heteroaryl, then R² is not aryl or heteroaryl;
- (h) when A is N-R⁴, Y is N, R¹ is H and R³ is alkyl, then X is not -NH₂;
- (i) when A is N-H or N-R⁴ and R² is H, then R³ is not
- 30 optionally substituted phenyl which is substituted by -N(R⁵)-(C₂-C₆ alkyl)-N(R⁵)₂ or -N(R⁵)-(C₂-C₆ alkyl)-Q;
- (j) when A is S, Y is N, R² is H, R³ is methyl or phenyl and R¹ is phenyl, NH₂, piperazinyl or methyl, then X is not NH₂, morpholinyl, 1-oxidothiomorpholinyl
- 35 or thiomorpholinyl;

- (k) when A is O, Y is C-H, R¹ is H, R² is H and R³ is propyl, butyl or hydroxypropyl, then X is not methyl, benzyl or methoxyphenyl-CH₂-;
- (l) when A is S, Y is N, R² is H or alkyl, R³ is methyl, then R¹ is not nitro-furyl, -NH-(C₂-C₁₀)alkyl-NH₂,
 5 -N(alkyl)-(C₂-C₁₀)alkyl-NH₂ or -N(methyl)-ethyl-NHSO₂-tolyl;
- (m) when A is S, Y is N, R² is H, halo, -NO₂ or alkyl, R³ is alkyl or phenyl and X is Q, -N(alkyl-OH)₂,
 10 -N(methyl)-ethyl-S-methyl or -N(methyl)-ethyl-S(O)-methyl, then R¹ is not Q, -N(alkyl-OH)₂, -N(methyl)-ethyl-S-methyl or -N(methyl)-ethyl-S(O)-methyl;
- (n) When A is O or S, Y is CH, R¹ is H and R² is H, then R³ is not -SO₂NH₂;
- (o) when A is S, Y is N, R¹ is H and R² is H, then (1) when R³ is phenyl, X is not -NH-NH₂, optionally substituted indolylalkylamino, optionally substituted indolylamino, optionally substituted thiazolidinonylamino or optionally substituted
 20 azetidinylamino, and (2) when R³ is methyl, X is not piperidinyl;
- (p) when A is O, Y is N, R¹ is optionally substituted phenyl, R² is H and R³ is alkyl, then X is not optionally substituted phenyl; and
- (q) R² is not an optionally substituted phenyl,
 25 pyridyl, pyrazinyl, pyrimidyl or pyridazinyl radical; and more preferably, R² is not an optionally substituted aryl or heteroaryl radical.

Another aspect of this invention is a key
 30 synthetic intermediate of formula



wherein A, R² and R³ are as defined above and W is -CN or -C(O)L; wherein L is a leaving group, such as a halo (preferably, bromo or chloro) or C1-C2 alkoxy radical.

In particular, in one aspect of the invention,
5 there is provided a method for the therapeutic or prophylactic treatment of obesity in a warm-blooded animal which comprises administering to a warm blooded animal in need thereof a therapeutically or prophylactically effective amount of a compound of this
10 invention.

In a related embodiment, there is provided a method for the treatment or prophylaxis of hyperphagia which comprises administering to a warm blooded animal in need thereof a therapeutically or prophylactically
15 effective amount of a compound of of this invention or a pharmaceutically acceptable salt, ester or solvate thereof. Likewise, there is provided a method for the inhibition of the desire to eat which comprises administering to a warm blooded animal in need thereof
20 an inhibition effective amount of a compound of this invention or a pharmaceutically acceptable salt, ester or solvate thereof.

In yet a further embodiment of the invention, given the relationship of obesity to diabetes, there is
25 provided a method for the treatment or prophylaxis of diabetes which comprises administering to a warm blooded animal a therapeutically or prophylactically effective amount of a compound of this invention, or a pharmaceutically acceptable salt, ester or solvate
30 thereof.

Given the apparent association of the NPY/NPY receptor signaling pathway, an additionally preferred embodiment of the invention includes a method for the therapeutic or prophylactic treatment of a NPY receptor
35 mediated disease state in a warm-blooded animal which comprises administering to said animal a

therapeutically or prophylactically effective amount of a compound of this invention, or a pharmaceutically acceptable salt, ester or solvate thereof. For example, the compounds of this invention may modulate a
5 neuropeptide Y receptor mediated response, for example, by antagonizing the NPY receptor response. Especially preferred in this embodiment is the inhibition of an NPY5 receptor response.

The compounds and pharmaceutical compositions of
10 this invention are useful in the prophylaxis and/or treatment (comprising administering to a mammal, such as a human, an effective amount of such compound, a pharmaceutically acceptable salt thereof, or composition) of (1) diseases and disorders which can be
15 effected or facilitated by modulating CRF, such as by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF; (2) diseases and disorders which can be effected or facilitated by modulating CRH binding protein, such as by inhibiting
20 CRH binding protein, including but not limited to disorders induced or facilitated by CRH binding protein; or (3) inflammatory disorders, such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder;
25 panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent
30 depression, child abuse induced depression, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's
35 disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency

virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa;

5 hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, nicotine, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome

10 of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including

15 stress induced immune dysfunctions (e.g., porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs);

20 muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; and hypoglycemia in mammals, including

25 humans.

CRF antagonists are effective in the prophylaxis and/or treatment of stress-related illnesses, mood disorders such as depression, major depressive disorder, single episode depression, recurrent

30 depression, child abuse induced depression, postpartum depression, dysthemia, bipolar disorders and cyclothymia; chronic fatigue syndrome; eating disorders such as anorexia and bulimia nervosa; generalized anxiety disorder; panic disorder; phobias; obsessive-

35 compulsive disorder, post-traumatic stress disorder, pain perception such as fibromyalgia; headache;

gastrointestinal diseases; hemorrhagic stress; ulcers;
stress-induced psychotic episodes; fever; diarrhea;
post-operative ileus, colonic hypersensitivity;
irritable bowel syndrome; Crohn's disease; spastic
5 colon; inflammatory disorders such as rheumatoid
arthritis and osteoarthritis; pain; asthma; psoriasis;
allergies; osteoporosis; premature birth; hypertension,
congestive heart failure; sleep disorders;
neurodegenerative diseases such as Alzheimer's disease,
10 senile dementia of the Alzheimer's type, multiinfarct
dementia, Parkinson's disease, and Huntington's
disease; head trauma; ischemic neuronal damage;
excitotoxic neuronal damage; epilepsy; stroke; spinal
cord trauma; psychosocial dwarfism; euthyroid sick
15 syndrome; syndrome of inappropriate antidiarrhetic
hormone; obesity; chemical dependencies and addictions;
drug and alcohol withdrawal symptoms; cancer;
infertility; muscular spasms; urinary incontinence;
hypoglycemia and immune dysfunctions including stress
20 induced immune dysfunctions, immune suppression and
human immunodeficiency virus infections; and stress-
induced infections in humans and animals.

CRH binding protein inhibitors are effective in
the prophylaxis and/or treatment of Alzheimer's disease
25 and obesity.

The compounds and pharmaceutical compositions of
this invention which inhibit the tyrosine kinase
activity of the receptor for the epidermal growth
factor (EGF) or of other protein tyrosine kinases are
30 useful in the prophylaxis and/or treatment of benign or
malignant tumors, effecting tumor regression,
preventing the formation of tumor metastases and the
growth of micrometastases, epidermal hyperproliferation
(psoriasis), neoplasias of epithelial character
35 (mammary carcinomas), and leukaemias. The compounds
and pharmaceutical compositions of this invention which

inhibit one or more protein tyrosine kinases and/or protein serine/threonine kinases are useful in the prophylaxis and/or treatment of those disorders of the immune system in which one or more protein tyrosine
5 kinases and/or protein serine/threonine kinases are involved and those disorders of the central or peripheral nervous system in which signal transmission by one or more protein tyrosine kinase and/or protein serine/threonine kinases are involved.

10 As utilized herein, the following terms shall have the following meanings:

"Alkyl", alone or in combination, means a saturated or partially unsaturated (provided there are at least two
15 carbon atoms) straight-chain or branched-chain alkyl radical containing the designated number of carbon atoms; preferably 1-15 carbon atoms (C_1 - C_{15}), more preferably 1-8 carbon atoms (C_1 - C_8), more preferably 1-6 carbon atoms (C_1 - C_6), more preferably 1-4 carbon
20 atoms (C_1 - C_4), more preferably 1-3 carbon atoms (C_1 - C_3), and most preferably 1-2 carbon atoms (C_1 - C_2). Examples of such radicals include methyl, ethyl, vinyl, n-propyl, allyl, isopropyl, n-butyl, 1-butenyl, 2-butenyl, 3-butenyl, sec-butyl, sec-butenyl, t-butyl,
25 n-pentyl, 2-methylbutyl, 3-methylbutyl, 3-methylbutenyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, and the like. A partially unsaturated alkyl preferably has at least one double or triple bond, more preferably
30 1-3 double or triple bonds, more preferably 1-2 double or triple bonds, and most preferably 1 double bond or 1 triple bond.

"Alkoxy", alone or in combination, means a radical of
35 the type "R-O-" wherein "R" is an alkyl radical as

defined above and "O" is an oxygen atom. Examples of such alkoxy radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, allyloxy and the like.

5

"Aryloxy-alkyl-", alone or in combination, means an alkyl radical as defined above wherein a hydrogen radical is replaced with a aryloxy radical, such as phenoxymethyl. "Alkyl-aryloxy-", alone or in
10 combination, means an aryloxy radical wherein a hydrogen radical of the aryl moiety is replaced with a alkyl radical, such as 4-methylphenoxy.

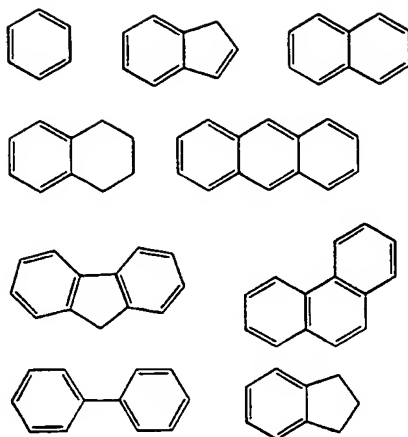
"Alkylthio", alone or in combination, means a radical
15 of the type "R-S-" wherein "R" is an alkyl radical as defined above and "S" is a sulfur atom. Examples of such alkylthio radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, allylthio and
20 the like.

The term "carbocyclic", alone or in combination, refers to an organic cyclic moiety in which the cyclic skeleton is comprised of only carbon atoms whereas the
25 term "heterocyclic", alone or in combination, refers to an organic cyclic moiety in which the cyclic skeleton contains one or more, preferably 1-4, more preferably 1-3, most preferably 1-2, heteroatoms selected from nitrogen, oxygen, or sulfur and which may or may not
30 include carbon atoms.

The term "cycloalkyl", alone or in combination, refers to a saturated or partially unsaturated (preferably 1-2 double bonds, more preferably 1 double bond)
35 carbocyclic moiety containing the indicated number of carbon atoms. The term "C₃-C₁₀ cycloalkyl", therefore,

refers to an organic cyclic substituent in which three to ten carbon atoms form a three, four, five, six, seven, eight, nine or ten-membered ring, including, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexenyl, cyclohexyl, cycloheptyl, cyclooctyl and the like ring. As used herein, "cycloalkyl" may also refer to two or more cyclic ring systems which are fused to form, for example, bicyclic, tricyclic, or other similar bridged compounds (e.g. adamantanyl).

"Aryl" refers to an aromatic carbocyclic group having a single ring, for example, a phenyl ring, multiple rings, for example, biphenyl, or multiple condensed rings in which at least one ring is aromatic, for example, naphthyl, 1,2,3,4,-tetrahydronaphthyl, anthryl, or phenanthryl, which can be unsubstituted or substituted with one or more (preferably 1-5, more preferably 1-4, more preferably 1-3, most preferably 1-2) other substituents as defined above. The substituents attached to a phenyl ring portion of an aryl moiety in the compounds of this invention may be configured in the ortho-, meta- or para- orientations. Examples of typical aryl moieties included in the scope of the present invention may include, but are not limited to, the following:



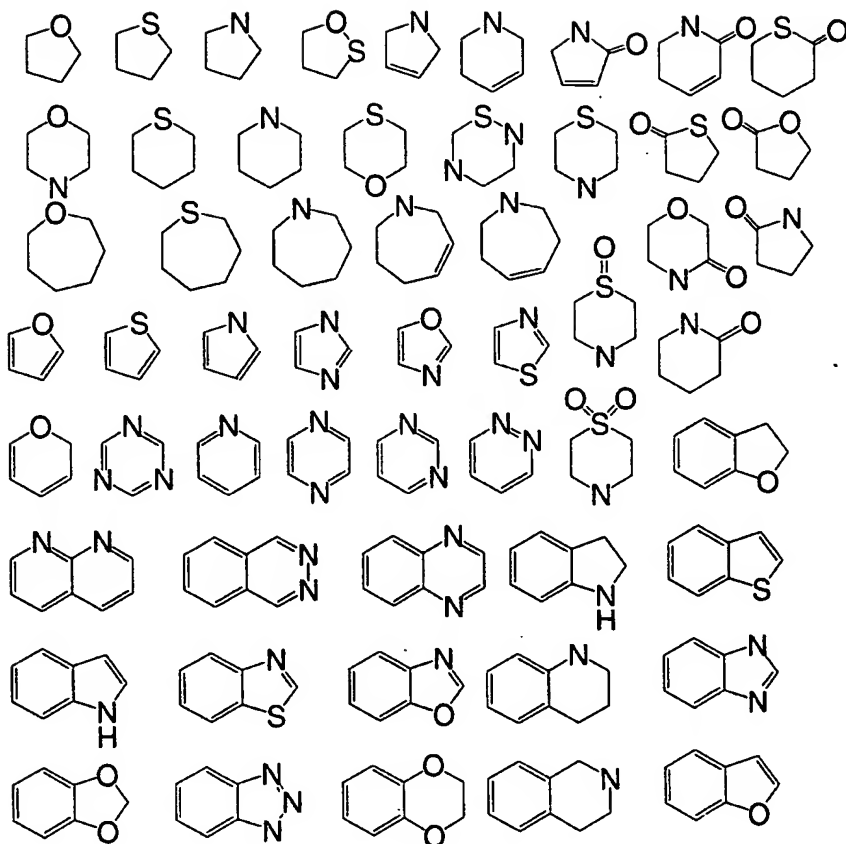
"Aryloxy" refers to an aryl group, as defined above, directly attached to an oxygen atom, which in turn is bonded to another atom. Thus, for example, benzyloxy, refers to a benzyl moiety linked through an oxygen atom to another substituent (e.g. -O-CH₂-phenyl).

"Heterocycle" or "heterocyclic" refers to a saturated, unsaturated or aromatic carbocyclic group having a single ring, multiple rings or multiple condensed rings, and having at least one hetero atom such as nitrogen, oxygen or sulfur within at least one of the rings. "Heteroaryl" refers to a heterocycle in which at least one ring is aromatic. Any of the heterocyclic or heteroaryl groups can be unsubstituted or optionally substituted with one or more groups as defined above and one or more, preferably 1-2, more preferably one, "oxo" group. Further, bi- or tri-cyclic heteroaryl moieties may comprise at least one ring which is either completely or partially saturated. "Heterocyclyl" refers to a saturated or partially unsaturated, preferably one double bond, monocyclic or bicyclic, preferably monocyclic, heterocycle radical containing at least one, preferably 1 to 4, more preferably 1 to 3, even more preferably 1-2, nitrogen, oxygen or sulfur

atom ring member and having preferably 3-8 ring members in each ring, more preferably 5-8 ring members in each ring and even more preferably 5-6 ring members in each ring. "Heterocyclyl" is intended to include sulfone
5 and sulfoxide derivatives of sulfur ring members and N-oxides of tertiary nitrogen ring members, and carbocyclic fused, preferably 3-6 ring carbon atoms and more preferably 5-6 ring carbon atoms.

As one skilled in the art will appreciate such
10 heterocyclic moieties may exist in several isomeric forms, all of which are to be encompassed by the present invention. For example, a 1,3,5-triazine moiety is isomeric to a 1,2,4-triazine group. Such positional isomers are to be considered within the
15 scope of the present invention. Likewise, the heterocyclic or heteroaryl groups can be bonded to other moieties in the compounds of the invention. The point(s) of attachment to these other moieties is not to be construed as limiting on the scope of the
20 invention. Thus, by way of example, a pyridyl moiety may be bound to other groups through the 2-, 3-, or 4-position of the pyridyl group. All such configurations are to be construed as within the scope of the present invention.

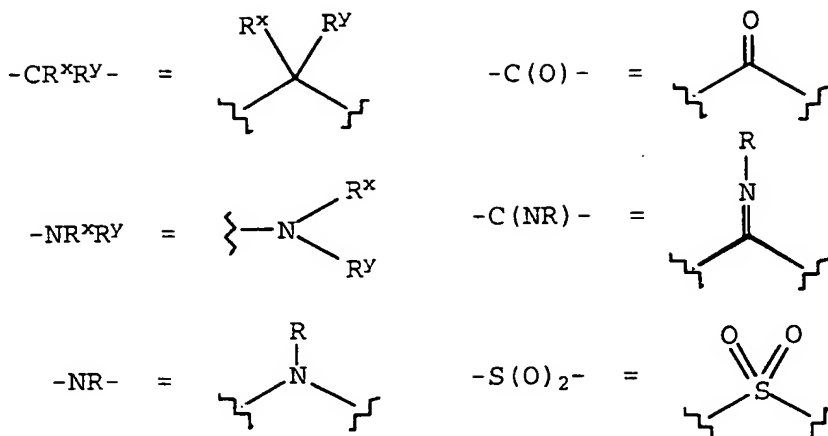
25 Examples of heterocyclic or heteroaryl moieties included in the scope of the present invention may include, but are not limited to, the following:



The term "halo" or "halogen" refers to a halogen atom which may include fluoro, chloro, bromo and iodo.

- 5 Preferred halo groups include chloro, bromo and fluoro with chloro and fluoro being especially preferred.

The symbols used above have the following meanings:



"Modulate" as used herein refers to the ability of a compound of this invention to interact with a receptor, target gene or other gene product to (a) up-regulate the activity of that receptor, target gene or other gene product or biological effect (for example, as an agonist) or (b) down-regulating the receptor, target gene or other gene product or other biological effect, particularly by acting as an antagonist for the receptor, target gene or other gene product.

Additionally, encompassed by "modulate" is the ability of a compound of the invention to effect a desired biological response, even if that response occurs upstream or downstream one or more steps in a signaling pathway from the receptor, target gene or other gene product in question. Thus, by way of example, the compounds of the invention may provide the desired effect by interacting with an NPY receptor, particularly an NPY5 receptor, to act as an agonist or antagonist to that receptor or at some point, either upstream or downstream, in the signaling pathway for the NPY receptor to effect the desired therapeutic or prophylactic response.

"Pharmaceutically acceptable salt", as used herein, refers to an organic or inorganic salt which is useful in the treatment of a warm-blooded animal. Such

salts can be acid or basic addition salts, depending on the nature of the compound of this invention. For examples of "pharmacologically acceptable salts," see Berge et al., J. Pharm. Sci. 66:1 (1977). As used
5 herein, "warm blooded animal" includes a mammal, including a member of the human, equine, porcine, bovine, murine, canine or feline species.

In the case of an acidic moiety in a compound of this invention, a salt may be formed by treatment of a
10 compound of this invention with a basic compound, particularly an inorganic base. Preferred inorganic salts are those formed with alkali and alkaline earth metals such as lithium, sodium, potassium, barium and calcium. Preferred organic base salts include, for
15 example, ammonium, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylamine, dibenzyl-ethylenediamine, and the like salts. Other salts of acidic moieties may include, for example, those salts formed with procaine,
20 quinine and N-methylglucosamine, plus salts formed with basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. An especially preferred salt is a sodium or potassium salt of a compound of this invention.

25 With respect to basic moieties, a salt is formed by the treatment of a compound of this invention with an acidic compound, particularly an inorganic acid. Preferred inorganic salts of this type may include, for example, the hydrochloric, hydrobromic, hydroiodic,
30 sulfuric, phosphoric or the like salts. Preferred organic salts of this type, may include, for example, salts formed with formic, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, d-glutamic, d-camphoric, glutaric, glycolic,
35 phthalic, tartaric, lauric, stearic, salicylic, methanesulfonic, benzenesulfonic, para-toluenesulfonic,

sorbic, puric, benzoic, cinnamic and the like organic acids. An especially preferred salt of this type is a hydrochloride or sulfate salt of a compound of this invention.

5 Also encompassed in the scope of the present invention are pharmaceutically acceptable esters of a carboxylic acid or hydroxyl containing group, including a metabolically labile ester or a prodrug form of a compound of this invention. A metabolically labile
10 ester is one which may produce, for example, an increase in blood levels and prolong the efficacy of the corresponding non-esterified form of the compound. A prodrug form is one which is not in an active form of the molecule as administered but which becomes
15 therapeutically active after some in vivo activity or biotransformation, such as metabolism, for example, enzymatic or hydrolytic cleavage. For a general discussion of prodrugs involving esters see Svensson and Tunek Drug Metabolism Reviews 165 (1988) and
20 Bundgaard Design of Prodrugs, Elsevier (1985). Amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases in vivo releasing the free drug and formaldehyde (Bungaard J. Med. Chem. 2503 (1989)). Also, drugs containing an
25 acidic NH group, such as imidazole, imide, indole and the like, have been masked with N-acyloxymethyl groups (Bundgaard Design of Prodrugs, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little, 4/11/81) discloses
30 Mannich-base hydroxamic acid prodrugs, their preparation and use. Esters of a compound of this invention, may include, for example, the methyl, ethyl, propyl, and butyl esters, as well as other suitable esters formed between an acidic moiety and a hydroxyl
35 containing moiety. Metabolically labile esters, may include, for example, methoxymethyl, ethoxymethyl, iso-

propoxymethyl, α -methoxyethyl, groups such as α -
((C₁-C₄)alkyloxy)ethyl; for example, methoxyethyl,
ethoxyethyl, propoxyethyl, iso-propoxyethyl, etc.; 2-
5 oxo-1,3-dioxolen-4-ylmethyl groups, such as 5-methyl-2-
oxo-1,3-dioxolen-4-ylmethyl, etc.; C₁-C₃ alkylthiomethyl
groups, for example, methylthiomethyl, ethylthiomethyl,
isopropylthiomethyl, etc.; acyloxymethyl groups, for
example, pivaloyloxymethyl, α -acetoxymethyl, etc.;
ethoxycarbonyl-1-methyl; or α -acyloxy- α -substituted
10 methyl groups, for example α -acetoxylethyl.

Additionally, the compounds of the invention may
have one or more asymmetric carbon atoms and,
therefore, may exist in stereoisomeric forms. All
stereoisomers are intended to be included within the
15 scope of the present invention. As used,
"stereoisomer" or "stereoisomeric" refers to a compound
which has the same molecular weight, chemical
composition, and constitution as another, but with the
atoms grouped such that their orientation in three-
20 dimensional space is different. Such stereoisomers may
exist as enantiomeric mixtures, diastereomers or may be
resolved into individual stereoisomeric components
(e.g. specific enantiomers) by methods familiar to one
skilled in the art.

25 Likewise, the compounds of this invention may
exist as isomers, that is compounds of the same
molecular formula but in which the atoms, relative to
one another, are arranged differently. In particular,
the alkylene substituents of the compounds of this
30 invention, are normally and preferably arranged and
inserted into the molecules as indicated in the
definitions for each of these groups, being read from
left to right. However, in certain cases, one skilled
in the art will appreciate that it is possible to
35 prepare compounds of this invention in which these

substituents are reversed in orientation relative to the other atoms in the molecule. That is, the substituent to be inserted may be the same as that noted above except that it is inserted into the

5 molecule in the reverse orientation. One skilled in the art will appreciate that these isomeric forms of the compounds of this invention are to be construed as encompassed within the scope of the present invention.

Further, the compounds of the invention may exist

10 as crystalline solids which can be crystallized from common solvents such as ethanol, N,N-dimethyl-formamide, water, or the like. Thus, crystalline forms of the compounds of the invention may exist as solvates and/or hydrates of the parent compounds or their

15 pharmaceutically acceptable salts. All of such forms likewise are to be construed as falling within the scope of the invention.

While it may be possible to administer a compound of the invention alone, in the methods described, the

20 compound administered normally will be present as an active ingredient in a pharmaceutical formulation. Thus, in one another embodiment of the invention, there is provided a formulation comprising a compound of this invention in combination with a pharmaceutically

25 acceptable carrier, diluent or excipient therefor.

The composition used in the noted therapeutic methods can be in a variety of forms. These include, for example, solid, semi-solid and liquid dosage forms, such as tablets, pills, powders, liquid solutions or

30 suspensions, liposomes, injectable and infusible solutions. The preferred form depends on the intended mode of administration and therapeutic application. Considerations for preparing appropriate formulations will be familiar to one skilled in the art and are

35 described, for example, in Goodman and Gilman's: "The Pharmacological Basis of Therapeutics", 8th Ed.,

Pergamon Press, Gilman et al. eds. (1990); and
"Remington's Pharmaceutical Sciences", 18th Ed., Mack
Publishing Co., A. Gennaro, ed. (1990). Methods for
administration are discussed therein, e.g. for oral,
5 topical, intravenous, intraperitoneal, or intramuscular
administration. Pharmaceutically acceptable carriers,
diluent, and excipients, likewise, are discussed
therein. Typical carriers, diluent, and excipients
may include water (for example, water for injection),
10 buffers, lactose, starch, sucrose, and the like.

As noted, a compound of the invention can be
administered orally, topically or parenterally (e.g.
intravenously, intraperitoneally, intramuscularly,
subcutaneously, etc.), or inhaled as a dry powder,
15 aerosol, or mist, for pulmonary delivery. Such forms
of the compounds of the invention may be administered
by conventional means for creating aerosols or
administering dry powder medications using devices such
as for example, metered dose inhalers, nasal sprayers,
20 dry powder inhaler, jet nebulizers, or ultrasonic
nebulizers. Such devices optionally may include a
mouthpiece fitted around an orifice. In certain
circumstances, it may be desirable to administer the
desired compound of the invention by continuous
25 infusion, such as through a continuous infusion pump,
or using a transdermal delivery device, such as a
patch.

The compounds of the invention may also be
administered as an aerosol. The term "aerosol"
30 includes any gas-borne suspended phase of a compound of
the invention which is capable of being inhaled into
the bronchioles or nasal passages. Specifically,
aerosol includes a gas-borne suspension of droplets of
the desired compound, as may be produced in a metered
35 dose inhaler or nebulizer, or in a mist sprayer.
Aerosol also includes a dry powder composition of a

compound of the instant invention suspended in air or other carrier gas, which may be delivered by insufflation from an inhaler device, for example.

For solutions used in making aerosols of the invention, the preferred range of concentration of the compounds of the invention is 0.1-100 milligrams (mg)/milliliter (mL), more preferably 0.1-30 mg/mL, and most preferably 1-10 mg/mL. Usually the solutions are buffered with a physiologically compatible buffer such as phosphate or bicarbonate. The usual pH range is from about 5 to about 9, preferably from about 6.5 to about 7.8, and more preferably from about 7.0 to about 7.6. Typically, sodium chloride is added to adjust the osmolarity to the physiological range, preferably within 10% of isotonic. Formulation of such solutions for creating aerosol inhalants is discussed, for example, in Remington's, supra; See, also, Ganderton and Johens, "Drug Delivery to the Respiratory Tract, Ellis Horwood (1987); Gonda, "Critical Review in Therapeutic Drug Carrier Systems" 6 273-313 (1990); and Raeburn et al. J. Pharmacol. Toxicol. Methods. 27 143-159 (1992).

Solutions of a compound of the invention may be converted into aerosols by any of the known means routinely used for making aerosol inhalant pharmaceuticals. In general, such methods comprise pressurizing or providing a means of pressurizing a container of the solution, usually with an inert carrier gas, and passing the pressurized gas through a small orifice, thereby pulling droplets of the solution into the mouth and trachea of the animal to which the drug is to be administered. Typically, a mouthpiece is fitted to the outlet of the orifice to facilitate delivery into the mouth and trachea.

In one embodiment, devices of the present invention comprise solutions of the compounds of the

invention connected to or contained within any of the conventional means for creating aerosols in asthma medication, such as metered dose inhalers, jet nebulizers, or ultrasonic nebulizers. Optionally such
5 devices may include a mouthpiece fitted around the orifice.

Further, there are provided a device which may comprise a solution of a compound of the instant invention in a nasal sprayer.

10 A dry powder comprising a compound of the invention, optionally with an excipient is another embodiment. This may be administered by a drug powder inhaler containing the described powder.

Powders may be formed with the aid of any suitable
15 powder bases, for example, talc, lactose, starch and the like. Drops may be formulated with an aqueous base or non-aqueous base also comprising one or more dispersing agents, suspending agents solubilizing agents, and the like.

20 Any of the formulations of the invention may also include one or more preservatives or bacteriostatic agents, for example, methyl hydroxybenzoate, ethyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chlorides, and the like. Additionally,
25 the formulations may contain other active ingredients.

The pharmaceutical formulations of the invention may be administered by parenteral or oral administration for prophylactic and/or therapeutic treatment. The pharmaceutical compositions can be
30 administered in a variety of unit dosage forms depending on the method of administration. For example, unit dosage forms suitable for oral administration may include, powders, tablets, pills, capsules and dragées.

35 The pharmaceutical formulations can be administered intravenously. Therefore, the invention

further provides formulations for intravenous administration which comprise a compound of the invention dissolved or suspended in a pharmaceutically acceptable carrier or diluent therefor. A variety of aqueous carriers can be used, for example, water, buffered water or other buffer solutions, saline, and the like. The resulting aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous solution prior to administration. The sterile aqueous solution for the lyophilized product can be packaged as a kit for use with the lyophilized formulation. The compositions can contain pharmaceutically acceptable substances to aid in administration and more closely mimic physiological conditions. Such substances, can include, for example, pH adjusting substances such as acids, bases or buffering agents, tonicity adjusting agents, wetting agents and the like. Such substances may include but are not limited to, for example, sodium hydroxide, hydrochloric acid, sulfuric acid, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, and the like or any other means familiar to one skilled in the art for maintaining pH at a desired level.

For solid formulations, carriers, diluents, and excipients known to one skilled in the art may be used. Such carriers, diluents and excipients may include, for example, mannitol, lactose, starch magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, or other solid polyol sugar, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable formulation is prepared by admixing any of the usual carrier, diluents, and excipients, such as those noted, with from about 0.1 to about 95% of a compound of the invention.

The preferred dosage for use in the methods of the invention, however, is in the range of about 0.01 mg/kg to about 100 mg/kg of body weight, preferably from about .1 mg/kg to about 50 mg/kg, up to 4 times per day. Whatever the dosage form, one skilled in the art will recognize that the dosage administered will be adjusted to factors such as the age, weight, and condition of the patient involved. The skilled practitioner will be familiar with how to adjust the dosage to accommodate these and other factors.

To better understand the synthesis of the compounds of this invention, Fig. 1 outlines a general reaction scheme for the synthesis of pyrrolo[3,2-d]pyrimidines of the invention. Fig. 2 also outlines a general reaction scheme for the synthesis of pyrrolo[3,2-d]pyridines and pyrrolo[3,2-d] pyrimidines while Fig. 3 provides a general process for the synthesis of thiopheno-, furano-, and pyrrolo-[3,2-d]-pyrimidines and -pyridines of the invention. Further, Fig. 4 provides a general process for the synthesis of 5-hydrocyclopenta-[2,1-d]pyrimidines of the invention.

The reactions described in the figures may be carried out in any number of solvents in which the reactants may be mutually soluble, including, for example, tetrahydrofuran, benzene, toluene, chloroform, dichloromethane, N,N-dimethylformamide, ethyl ether, dioxane, water, acetonitrile, or the like. Generally the reaction is carried out at a temperature of between -80°C and 150°C, preferably, however, at room temperature. In certain cases, as noted in the examples provided herein, however, the temperature of the reaction may reach as high as or exceed about 360°C.

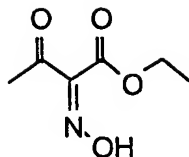
The product and intermediates may be isolated or purified using one or more standard purification techniques, including, for example, one or more of

simple solvent evaporation, recrystallization, distillation, sublimation, filtration, chromatography, including thin-layer chromatography, HPLC (e.g. reverse phase HPLC using, for example, dilute trifluoroacetic acid in water, acetonitrile, or methanol mixtures as eluent), column chromatography, flash chromatography, radial chromatography, trituration, and the like.

In the preparation of the compounds of the invention, one skilled in the art will understand that one may need to protect or block various reactive functionalities on the starting compounds or intermediates while a desired reaction is carried out on other portions of the molecule. After the desired reactions are complete, or at any desired time, normally such protecting groups will be removed by, for example, hydrolytic or hydrogenolytic means. Such protection and deprotection steps are conventional in organic chemistry. One skilled in the art is referred to "Protective Groups in Organic Chemistry," McOmie, Ed., Plenum Press, New York, New York; and "Protective Groups in Organic Synthesis," Greene, Ed., John Wiley & Sons, New York, NY (1981) for the teaching of protective groups which may be useful in the preparation of compounds of the present invention.

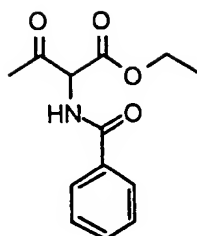
Alternate means beyond those described above for preparing the compounds of the invention will be apparent to one skilled in the art and the noted general procedures are not to be construed as limiting the invention. To more fully understand the invention, including methods of preparing compounds of the invention, the following non-limiting examples are provided. The reader will appreciate that starting materials not otherwise described herein are either available commercially or can be prepared by methods generally known in the art.

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Anhydrous solvents such as dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and toluene, dioxane were obtained from Aldrich Chemical Company in Sure/Seal bottles. All reactions involving air- or moisture-sensitive compounds were performed under a N_2 atmosphere. Flash chromatography was performed using ICN Biomedicals (SiliTech 32-63D 60A). Thin-layer chromatography (TLC) was performed with Analtech or Whatman silica gel TLC plates (250 μm). Preparatory TLC was performed with Whatman silica gel TLC plates (2000 μm). ^1H NMR spectra were determined with superconducting FT NMR spectrometers operating at 400 and 500 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^1H NMR data are reported in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; quin, quintet), number of protons, and coupling constants in Hz. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Melting points were determined with a Buchi 535 capillary melting point apparatus and are uncorrected. Low resolution mass spectra (MS) were determined on a Perkin Elmer-SCIEX API 165 mass spectrometer using APCI or ES ionization modes (positive or negative). High resolution mass spectra (HRMS) were performed by Mass Consortium, San Diego, CA using FAB ionization.

**Example 1****(a) Ethyl 2-(hydroxyimino)-3-oxobutanoate.**

A solution of ethyl acetoacetate (Aldrich Chemical Company) (37.5g, 0.279 mol) in acetic acid (55 mL) was cooled in an ice-water bath. A solution of sodium nitrite (26.5 g, 0.384 mol) in distilled H₂O (60 mL) was added to the cooled reaction mixture over a 0.5 h period via a pressure-equalizing addition funnel. Upon this addition, the colorless reaction mixture turned a red-orange color. The cold bath was removed and the solution was allowed to stir at room temperature for 2 h. The red solution was transferred to a separatory funnel and extracted with Et₂O (3 x 100 mL). The organic extracts were placed in a 1-L beaker equipped with a magnetic stirring bar. Saturated aqueous NaHCO₃ was added and the solution was stirred vigorously. Additional portions of solid NaHCO₃ were added to neutralize the solution. The aqueous layer was separated and extracted with ether. The organic layers were combined, washed with water and saturated NaCl, and dried over MgSO₄. The solution was filtered and concentrated with a rotary evaporator to give 42.5 g (95%) of the title compound as a pale yellow oil. ¹H NMR (CDCl₃; 500 MHz): δ 1.36 (t, 3, J = 7.1), 2.42 (s, 3), 4.39 (q, 2, J = 7.1), 9.05 (m, 1). MS m/z : 160 (M+1). This material was used without further purification.

53

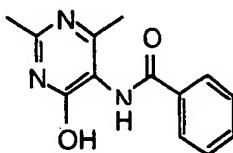


(b) Ethyl 3-oxo-2-(phenylcarbonylamino)butanoate.

To a 1-L, round-bottomed flask was added ethyl 2-(hydroxyimino)-3-oxybutyrate (25.0 g, 0.157 mol), H₂SO₄ (30% w/v) (230 mL) and crushed ice (250 g). This solution was cooled in an ice-salt-water bath and the internal temperature was monitored with an alcohol thermometer. Powdered zinc (100 mesh - Aldrich Chemical Company) (30.0 g, 0.459 mol, 2.9 equiv) was added to this cooled solution portionwise via a powder addition funnel. The temperature of the reaction was maintained between 0-10 °C. After the addition of the zinc was complete the reaction mixture was allowed to stir at 0 °C for 0.5 h. The solution was filtered through a fritted funnel into a clean 1-L round-bottomed flask. This clear, colorless solution was cooled in an ice-water bath and sodium acetate trihydrate (Aldrich Chemical Company) (162.5 g, 1.19 mol) was added with stirring. Benzoyl chloride (Aldrich Chemical Company) (18.3 mL, 22.1 g, 0.157 mol) was slowly added to the resulting cloudy solution via a syringe. After the addition was complete, the cold bath was removed and the solution was allowed to stir at room temperature for 24 h. The yellow reaction mixture was extracted with CH₂Cl₂ (3 x 100 mL). The organic layers were washed with saturated aqueous NaHCO₃, dried over MgSO₄, filtered, and concentrated on a rotary evaporator to give 30.3 g of a yellow oil. This material was purified by flash chromatography on silica gel with 4:1 hexanes: EtOAc as eluant to give 20.0 g (51%) of the title compound as a viscous pale-

yellow oil. ¹H NMR (CDCl₃; 500 MHz): δ 1.33 (t, 3, J = 7.1), 2.46 (s, 3), 4.31 (m, 2), 5.43 (d, 1, J = 6.4), 7.28 (br m, 1), 7.46 (t, 2, J = 7.6), 7.54 (m, 1), 7.85 (d, 2, J = 7.2). MS m/z: 250 (M+1), 178 (base).

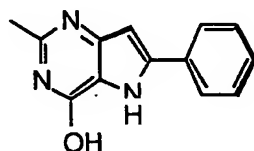
5



(c) 2,6-Dimethyl-4-hydroxy-5-benzamidopyrimidine.

Absolute EtOH (150 mL) was added to an oven-dried round-bottomed flask, and small pieces of sodium (4.95 g, 0.215 mol) were added portionwise. A reflux condenser was attached to the flask and the solution was allowed to stir at room temperature until all of the sodium was consumed. Acetamidine hydrochloride (Aldrich Chemical Company) (9.95 g, 0.105 mol) was added in one portion and the resulting creamy white solution was allowed to stir at room temperature for 0.5 h. In a separate flask ethyl 3-oxo-2-(phenyl carbonylamino)butanoate (23.8 g, 0.956 mol) was dissolved in absolute EtOH (30 mL). The acetamidine solution was filtered through a plug of celite into the ketoester solution. As this solution was added, the reaction mixture turned from an orange to a dark brown color. The mixture was placed under a N₂ atmosphere and allowed to stir at room temperature overnight. As the reaction proceeded solids precipitated out of solution to give a thick brown-orange mixture. The reaction mixture was filtered through a fritted funnel and the solids were washed with EtOH. The solids were dissolved in distilled H₂O and HCl (conc.) was added to acidify the solution to a pH of 4-5 (pH paper). Upon acidification solids precipitated out of solution. The solution was cooled in an ice-water bath, the solids

were filtered, washed with cold water and dried in a vacuum oven to give 7.59 g (33%) of the title compound as a white powder. The EtOH filtrate was concentrated with a rotary evaporator to give 13 g of a sticky orange oil. This material was purified by flash chromatography on silica gel with 95:5 CH₂Cl₂:MeOH as eluant to give an additional 2.61 g (11%) of the title compound as fluffy pale-yellow flakes (total yield 10.2 g (44%)). Mp: 279-281 °C. (lit. mp = 282 °C; (E.A. Falco et al., *J. Am. Chem. Soc.*, **1952**, 74, 4897-4902). ¹H NMR (DMSO-d₆; 500 MHz): δ 2.09 (s, 3), 2.28 (s, 3), 7.51 (t, 2, *J* = 7.1), 7.58 (t, 1, *J* = 7.2), 7.96 (d, 2, *J* = 7.4), 9.51 (s, 1), 12.51 (br s, 1). MS *m/z* : 244 (M+1). Anal. Calcd for C₁₃H₁₃N₃O₂: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.10, H, 5.40, N, 17.19.



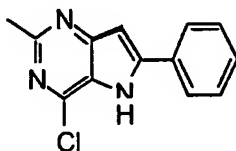
(d) 2-Methyl-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol.

Method A: To an oven-dried, 250-mL, round-bottomed flask was added absolute EtOH (45 mL). Small pieces of sodium metal (2.87 g, 0.125 mol) were added portionwise. After all of the sodium was consumed, 2, 6-dimethyl-4-hydroxy-5-benzamidopyrimidine (10.1 g, 41.7 mol) was added in one portion via a powder addition funnel. An additional portion of EtOH (20 mL) was added to rinse the last portion of the amide from the funnel. The reaction mixture was heated at reflux for 0.25 h until all of the solids dissolved to give an orange solution. The condenser was replaced with a short-path distillation head and the EtOH was distilled off under a N₂ atmosphere. The resulting solids were scraped off the sides of the flask with a spatula and heated with a heating mantle at 360 °C for 20 min. The

residue was allowed to cool to room temperature, dissolved in distilled H₂O (35 mL), and HCl (conc.) was added portionwise to adjust the pH of the solution to 4-5 (pH paper). The resulting precipitate was filtered and dried in a vacuum oven to give 6.38 g of a tan solid. This material was dissolved in 3 N NaOH (~30 mL), and the resulting dark brown solution was filtered through a fritted funnel. Acetic acid was added to the filtrate with stirring. The resulting solids were filtered, washed with distilled H₂O, recrystallized from EtOH and dried in a vacuum oven to give 1.45 g (15%) of the title compound as a tan powder. Mp: >280 °C (lit mp = 322(dec.); K. Tanaka et al., *Chem. Pharm. Bull.* 1964, 12, 1024-1030). ¹H NMR (DMSO-d₆; 400 MHz): δ 2.31 (s, 3), 6.77 (d, 1, J = 2.2), 6.77 (d, 1, J = 2.2), 7.36 (tm, 1, J = 6.5), 7.43 (t, 2, J = 7.6), 7.93 (dd, 2, J = 1.4, 7.2), 11.80 (s, 1), 12.28 (s, 1). MS m/z : 226 (M+1). Anal. Calcd for C₁₃H₁₁N₃O: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.24; H, 5.97; N, 18.58.

Method B: To an oven-dried, 100-mL, round-bottomed flask equipped with a glass-covered magnetic stir bar was added absolute EtOH (35 mL). Small pieces of sodium metal (Aldrich Chemical Company) (1.89 g, 0.082 mol) were added portionwise. After all of the sodium was consumed, 2,6-dimethyl-4-hydroxy-5-benzamido pyrimidine (5.0 g, 0.02 mol) was added in one portion via a powder addition funnel. An additional portion of EtOH (2 mL) was added to rinse the last portion of the amide from the funnel. A reflux condenser was attached to the flask and the mixture was heated at reflux for 0.5 h until all of solid dissolved to give a yellow solution. The reflux condenser was replaced with a short-path distillation head and the EtOH was distilled off under a N₂ atmosphere. The resulting yellow solids were heated with a sand bath at 340 °C for 15-20 min.

The residue was allowed to cool to room temperature and dissolved in distilled water (50 mL). The resulting brown solution, which contained black pieces of solids, was filtered through a Buchner funnel into a round-bottomed flask. An additional portion of water (50 mL) was added to rinse the reaction flask. The dark-brown solution (pH = 12) was transferred to a 250-mL beaker. HCl (conc.) was added dropwise to adjust the pH of the solution to 4-5 (pH paper). Precipitate formed instantly upon acidification. The suspension was stirred for 2 h, filtered, washed by cold water and dried in a vacuum oven at 40 °C overnight to give 3.20 g (69%) of the title compound as a fine tan powder (98 % pure by HPLC). ¹H NMR of this material was identical to that obtained in Method A. This material was used without further purification.

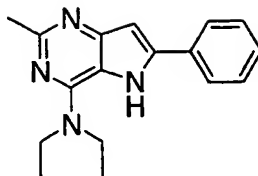


(e) 4-Chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine.

Method A: Phosphorus oxychloride (Aldrich Chemical Company) (2.46 mL, 4.05 g, 26.4 mmol), N,N-diethylaniline (Aldrich Chemical Company) (1.2 mL, 1.12 g, 7.5 mmol), 1,2-dichloroethane (4 mL) and 2-methyl-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol (0.50 g, 2.22 mmol) were added to a 50-mL, oven-dried, round-bottomed flask. The resulting dark-red solution was placed under N₂ and heated at reflux for 3 h. The solution was concentrated with a rotary evaporator to give a dark red oil. This material was cooled in an ice-water bath and distilled H₂O was added. The solution was filtered through a fritted funnel, and the filtrate was concentrated with a rotary evaporator to give a wet

solid. This crude material was free based by the addition of aqueous NH_4OH and extracted into EtOAc. The organic layer was dried over MgSO_4 , filtered and concentrated with a rotary evaporator to give 0.98 g of
5 an orange oil. This material was purified by flash chromatography on silica gel with 4:1 hexanes:EtOAc followed by 1:1 hexanes:EtOAc as eluant to give 0.24 g (44%) of the title compound as a tan solid. ^1H NMR (CDCl_3 ; 400 MHz) : δ 2.76 (s, 3), 6.90 (s, 1), 7.43 (m,
10 3), 7.80 (dm, 2, $J = 6.5$), 10.17 (br s, 1). MS m/z : 243 (M^+), 208 (base).

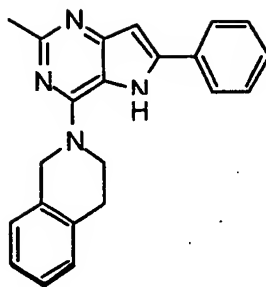
Method B: Phosphorus oxychloride (Aldrich Chemical Company) (30 mL, 0.322 mol) was added to a 100-mL, oven-dried, round-bottomed flask containing a magnetic
15 stir bar and 2-methyl-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol (2.8 g, 0.012 mol). The resulting dark-red solution was heated at 120 °C and the reaction was monitored by HPLC. When the starting material was totally consumed (~24 h) the solution was concentrated
20 with a rotary evaporator to give a dark red oil. This material was cooled in an ice-water bath and 100 mL of ice- NH_4OH - H_2O was added. HCl (conc.) was added dropwise to adjust the pH to 7-8 (pH paper). The neutralized solution was extracted into 200 mL of EtOAc. The
25 organic layer was dried over MgSO_4 , filtered, concentrated with a rotary evaporator and dried in a vacuum oven at 40 °C overnight to give 2.21 g (73%) of the title compound as a tan solid (94 % pure by HPLC). ^1H NMR of this material was identical to that obtained
30 in Method A. This material was used without further purification.



(f) Diethyl(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amine.

Diethylamine (Aldrich Chemical Company) (0.66 mL, 0.47 g, 6.4 mmol), distilled H₂O (15 mL), 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (0.24 g, 0.98 mmol) and K₂CO₃ (0.68 g, 4.92 mmol) were added to a round-bottomed flask and placed under a N₂ atmosphere. The resulting suspension was heated at reflux for 6 h. Additional portions of diethylamine (1.32 mL, 13 equiv) and K₂CO₃ (0.68 g) were added and the reaction was heated at reflux overnight. The solution was allowed to cool to room temperature and CH₂Cl₂ was added. The organic layer was separated, dried over MgSO₄, filtered and concentrated with a rotary evaporator to give 0.24 g of a light orange solid. This material was purified by flash chromatography on silica gel with 1:1 hexanes:EtOAc as eluant to give 0.19 g (68%) of the title compound as an off-white powder. Mp: 184-185 °C (lit mp = 183-185 °C; G.A. Modnikova et al., *Pharm. Chem. J.*, 1988, 22, 135-141). ¹H NMR (CDCl₃; 500 MHz): δ 1.37 (t, 6, J = 7.0), 2.57 (s, 3), 3.77 (q, 4, J=7.0), 6.75 (s, 1), 7.38 (t, 1, J = 7.3), 7.47 (t, 2, J = 7.5), 7.63 (d, 2, J = 7.6), 8.13 (br s, 1). MS m/z : 281 (M+1). Anal Calcd for C₁₇H₂₀N₄: C, 72.83; H, 7.19; N, 19.98. Found: C, 73.02; H, 7.26; N, 19.76.

60

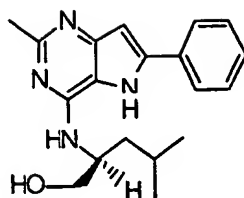
**Example 2****2-Methyl-6-phenyl-4-(2-1,2,3,4-tetrahydroquinolino-2-yl)pyrrolo[3,2-d]pyrimidine.**

5 To a 5-mL Wheaton vial was added was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (100 mg, 0.41 mmol) and 1,2,3,4-tetrahydroquinoline (Aldrich Chemical Company) (0.26 mL, 2.05 mmol). A solution of K_2CO_3 (0.567 g, 4.1 mmol) in H_2O (2.5 mL) was added, the vial was securely capped, and the reaction mixture was heated at 120 °C for 4 h. After cooling to room temperature, EtOAc (1 mL) was added. The resulting precipitate was collected by filtration, washed with distilled H_2O and EtOAc, and

10 dried in a vacuum oven to give 105 mg (75%) of the title compound as an off-white solid. Mp: 251-253 °C (dec.). 1H NMR ($CDCl_3$; 400 MHz): δ 2.63 (s, 3), 3.09 (t, 2, $J = 5.9$), 4.13 (t, 2, $J = 5.9$), 5.02 (s, 2), 6.78 (s, 1), 7.21-7.25 (m, 4), 7.38-7.50 (m, 3), 7.66 (d, 2, $J = 7.3$), 8.37 (br s, 1). MS m/z : 341 (M+1), 339 (M-1). Anal. Calcd for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.55; H, 5.91; N, 16.42.

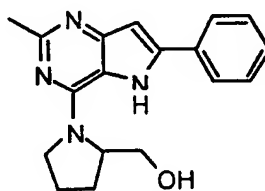
15
20

61

**Example 3**

(S)-4-Methyl-2-[(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amino]pentan-1-ol.

- 5 This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (100 mg, 0.41 mmol), (S)-(+)-leucinol (Aldrich Chemical Company) (0.26 mL, 2.05 mmol) and K_2CO_3 (0.567 g, 4.1 mmol) in H_2O (2.5 mL) to give 75 mg (56%) of the title compound as shiny off-white crystals. Mp: 267-269 °C (dec.). 1H NMR ($DMSO-d_6$; 400 MHz): δ 0.91-0.95 (m, 6), 1.48-1.52 (m, 2), 1.66-1.70 (m, 1), 2.37 (s, 3), 3.50 (br s, 2), 4.39 (br s, 1), 4.90 (br s, 1), 6.65 (d, 1, $J = 8.4$), 6.72 (s, 1), 7.36-7.52 (m, 3), 7.79 (d, 2, $J = 7.9$), 11.35 (br s, 1). MS m/z : 325 ($M+1$), 323 ($M-1$). Anal. Calcd for $C_{19}H_{24}N_4O$: C, 70.34; H, 7.46; N, 17.27. Found: C, 70.14; H, 7.35; N, 17.13.
- 10
15

**Example 4**

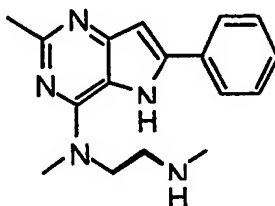
(S)-[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)pyrrolidin-2-yl]methan-1-ol.

- 20 This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (70 mg, 0.287 mmol), (S)-(+)-2-pyrrolidinemethanol (Aldrich Chemical Company) (0.14 mL, 1.44 mmol) and K_2CO_3 (0.397
- 25

g, 2.87 mmol) in H₂O (2 mL) to give 61.9 mg (70%) of the title compound as an off-white solid. An analytical sample was obtained by recrystallization from EtOH.

Mp: 255-256 °C. ¹H NMR (CDCl₃; 500 MHz): δ 2.06-2.14

5 (m, 4), 2.54 (s, 3), 3.76 (d, 1, *J* = 9.23), 3.84 (dd, 1, *J* = 2.0, 11.1), 3.96-3.98 (m, 1), 4.11 (q, 1, *J* = 7.6, 7.9), 4.55-4.57 (m, 1), 6.68 (s, 1), 7.35-7.45 (m, 3), 7.61 (d, 2, *J* = 7.4), 9.17 (br s, 1). MS *m/z*: 167 (base), 307 (M-1). Anal. Calcd for C₁₈H₂₀N₄O: C, 70.11;
10 H, 6.54; N, 18.17. Found: C, 70.00; H, 6.59; N, 18.11.

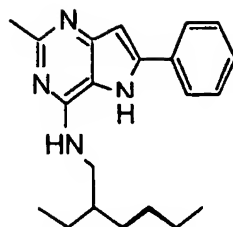


Example 5

Methyl[2-(methyamino)ethyl](2-methyl-6-phenyl)
15 **pyrrolo[2,3-e]pyrimidin-4-yl)amine.**

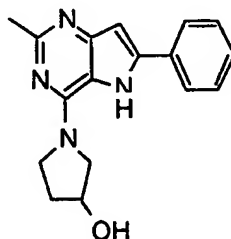
This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (70 mg, 0.29 mmol), *N,N'*-dimethylethylenediamine (Aldrich
20 Chemical Company) (0.15 mL, 1.44 mmol) and K₂CO₃ (0.40 g, 2.87 mmol) in H₂O (2 mL). The crude material was purified by flash chromatography on silica gel with 9:1 CHCl₃:MeOH as eluant to give 18.5 mg (22%) of the title compound as an off-white solid. An analytical sample
25 was obtained by recrystallization from EtOH. ¹H NMR (CDCl₃; 400 MHz): δ 2.60 (s, 6), 3.04 (t, 2, *J* = 4.5), 3.15 (s, 3), 3.75 (t, 2, *J* = 4.5), 6.76 (s, 1), 7.31-7.42 (m, 3), 7.70 (d, 2, *J* = 7.4). MS *m/z*: 296 (M+1), 294 (M-1). HRMS: Calcd for M+H: 296.1875. Found:
30 296.1884.

63

**Example 6**

(2-Ethylhexyl)(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amine.

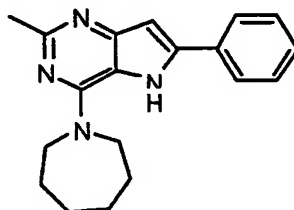
5 This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (70.0 mg, 0.29 mmol), 2-ethylhexylamine (Aldrich Chemical Company) (0.24 mL, 1.44 mmol) and K_2CO_3 (0.40 g, 2.87 mmol) in H_2O (2 mL) to give 61 mg (63%) of the title compound as a white solid. An analytical sample was obtained by recrystallization from *i*-PrOH. Mp: 288-289 °C (dec.). 1H NMR ($CDCl_3$; 500 MHz): δ 0.72-0.78 (m, 6), 1.15-1.34 (m, 9), 2.62 (s, 3), 3.56 (dd, 2, J = 5.3, 7.6), 6.71 (s, 2), 7.17-7.24 (m, 3), 7.59 (d, 2, J = 7.6), 12.78 (br s, 1). MS m/z : 337 ($M+1$), 335 ($M-1$). HRMS: Calcd for $M+H$: 337.2392. Found: 337.2397.

**Example 7**

1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)pyrrolidin-3-ol.

20 This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (70.0 mg, 0.29 mmol), 3-pyrrolidinol (Aldrich Chemical

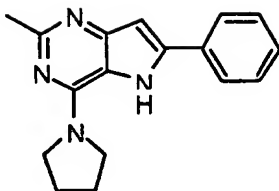
Company) (0.12 mL, 1.44 mmol) and K_2CO_3 (0.40 g, 2.87 mmol) in H_2O (2 mL). The crude material was purified by flash chromatography on silica gel with 10:1 $CHCl_3$:MeOH as eluant to give 30.9 mg (37%) of the title compound
5 as an off-white solid. An analytical sample was obtained by recrystallization from EtOH. Mp: 234-235 °C. 1H NMR ($DMSO-d_6$; 500 MHz): δ 1.96-2.05 (m, 2), 2.39 (s, 3), 3.77-3.93 (m, 4), 4.43 (s, 1), 5.03 (s, 1), 6.71 (s, 1), 7.38-7.50 (m, 3), 7.88 (d, 2, $J = 7.6$),
10 10.64 (br s, 1). MS m/z : 295 (M+1), 293 (M-1). HRMS: Calcd for M+H: 295.1923. Found: 295.1910.



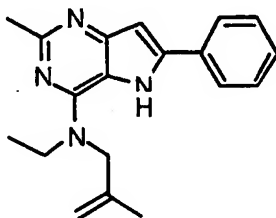
Example 8

15 4-Homopiperidyl-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (70 mg,
20 0.287 mmol), hexamethyleneimine (Aldrich Chemical Company) (0.16 mL, 1.44 mmol) and K_2CO_3 (0.40 g, 2.87 mmol) in H_2O (2 mL). The crude material was purified by preparative TLC on silica gel with 9:1 $CHCl_3$:MeOH as eluant to give 54.1 mg (62%) of the title compound as a
25 white solid. An analytical sample was obtained by recrystallization from EtOAc. Mp: 209-210 °C. 1H NMR ($CDCl_3$; 500 MHz): δ 1.65-1.68 (m, 4), 1.93-1.97 (m, 4), 2.57 (s, 3), 3.91 (t, 4, $J = 5.9$), 6.75 (s, 1), 7.37-7.49 (m, 3), 7.63 (d, 2, $J = 7.43$), 8.19 (br s, 1). MS
30 m/z : 307 (M+1), 305 (M-1). HRMS: Calcd for M+H: 307.1923. Found: 307.1933.

**Example 9****2-Methyl-6-phenyl-4-pyrrolidinylpyrrolo[3,2-d]pyrimidine.**

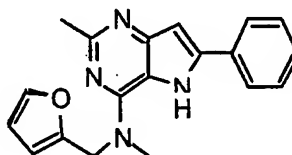
This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (70 mg, 0.287 mmol), pyrrolidine (Aldrich Chemical Company) (0.12 mL, 1.44 mmol) and K_2CO_3 (0.397 g, 2.87 mmol) in H_2O (2 mL). The crude material was purified by flash chromatography on silica gel with 20:1 $CHCl_3$:MeOH as eluant to give 42.1 mg (53%) of the title compound as an off-white solid. An analytical sample was obtained by recrystallization from EtOH. 1H NMR ($CDCl_3$; 500 MHz): δ 2.07 (t, 4, $J = 6.3$), 2.58 (s, 3), 3.88-3.90 (m, 4), 6.71 (s, 1), 7.36-7.46 (m, 3), 7.63 (d, 2, $J = 7.7$). MS m/z : 279.5 (M+1), 277.5 (M-1). HRMS: Calcd for M+H: 279.1610. Found: 279.1613.

**Example 10****Ethyl(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(2-methylprop-2-enyl)amine.**

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (70 mg,

0.29 mmol), *N*-ethyl-2-methylallylamine (Aldrich Chemical Company) (0.19 mL, 1.44 mmol) and K_2CO_3 (0.397 g, 2.87 mmol) in H_2O (2 mL). The crude material was purified by preparative TLC on silica gel with 1:1
5 EtOAc:hexanes as eluant to give 36.7 mg (42%) of the title compound as off-white solid. An analytical sample was obtained by recrystallization from EtOAc. Mp: 148-150 °C. 1H NMR ($CDCl_3$; 500 MHz): δ 1.32 (t, 3, J = 7.1), 1.95 (s, 3), 2.59 (s, 3), 3.78 (q, 2, J =
10 7.1), 4.20 (s, 2), 5.18 (s, 1), 5.24 (s, 1), 6.74 (s, 1), 7.35-7.48 (m, 3), 7.55 (d, 2, J = 7.4), 8.47 (br s, 1). MS m/z : 307 (M+1), 305 (M-1). Anal. Calcd for $C_{19}H_{22}N_4$: C, 74.48; H, 7.24; N, 18.28. Found: C, 74.36; H, 7.27; N, 18.19.

15

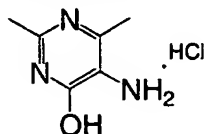
**Example 11**

(2-Furylmethyl)methyl(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amine.

20 This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (70.0 mg, 0.29 mmol), *N*-methylfurfurylamine (The Sigma-Aldrich Library of Rare Chemicals) (0.16 g, 1.44 mmol)
25 and K_2CO_3 (0.40 g, 2.87 mmol) in H_2O (2 mL). The crude material was purified by preparative TLC on silica gel with 1:1 EtOAc:hexanes as eluant to give 53.6 mg (59%) of the title compound as an off-white solid. An analytical sample was obtained by recrystallization
30 from EtOAc. Mp: 168-169 °C. 1H NMR ($CDCl_3$; 500 MHz): δ 2.62 (s, 3), 3.35 (s, 3), 4.83 (s, 2), 6.42-6.44 (m, 2), 6.79 (s, 1), 7.36-7.48 (m, 4), 7.64 (d, 2, J =

7.2), 8.91 (br s, 1). MS m/z : 319.5 (M+1), 317.0 (M-1). HRMS: Calcd for M+H: 319.1559. Found: 319.1566.

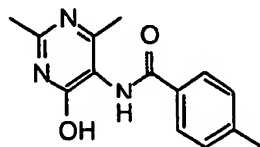
Example 12



5

(a) 5-Amino-2,6-dimethyl-4-hydroxypyrimidine Hydrochloride.

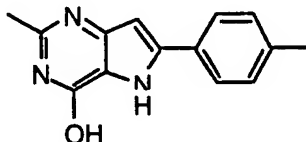
To a 150-mL round-bottomed flask was added 5-acetamido-2,6-dimethyl-4-hydroxypyrimidine (Example 46
10 (b)) (6.0 g, 32.8 mmol) and HCl (conc.) (25 mL). The cloudy suspension was heated at reflux for 5 h. The solution became clear upon heating. The reaction mixture was allowed to cool to room temperature and then concentrated using the rotary evaporator. The
15 white solid residue was triturated with acetone (25 mL) and the solid collected by vacuum filtration. The resulting solid was boiled in hot MeOH, hot filtered, and dried in a 60 °C vacuum oven to give 5.0 g (87%) of the title compound as a white solid. ^1H NMR (DMSO- d_6 ;
20 400 MHz): δ 2.24 (s, 3), 2.48 (s, 3). MS m/z : 140 (M+1).



(b) 2,6-Dimethyl-4-hydroxy-5-(p-toluamido)pyrimidine.

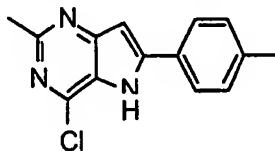
4-Dimethylaminopyridine (DMAP) (2.69 g, 22.0 mmol)
25 and 1,3-diisopropylcarbodiimide (DIC) (3.3 mL, 21.0 mmol) were added to a solution of p-toluic acid (2.72 g, 20 mmol) in CH_2Cl_2 (30 mL) and DMF (2 mL) at 0 °C under nitrogen. After stirring at 0 °C for 10 min, 5-amino-2,6-dimethyl-4-hydroxypyrimidine hydrochloride
30 (3.51 g, 20.0 mmol) was added in one portion. The

resulting mixture was stirred at 0 °C for 1 h and at room temperature for 16 h. The thick precipitate that formed was collected by filtration, washed with CH₂Cl₂ (20 mL), and EtOH (20 mL). This material was dried in a vacuum oven overnight to give 3.25 g (63%) of the title compound as a white solid. ¹H NMR (DMSO-d₆; 500 MHz): δ 2.08 (s, 3), 2.29 (s, 3), 2.38 (s, 3), 7.31 (d, 2, J = 7.9), 7.89 (d, 2, J = 7.8), 9.51 (br s, 1), 12.60 (br s, 1). This material was used without further purification.



(c) 2-Methyl-6-(4-methylphenyl)pyrrolo[3,2-d]pyrimidin-4-ol.

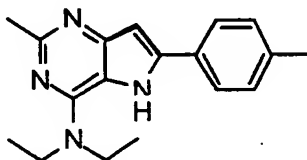
This material was prepared according to the method described in Example 1(d) using 2,6-dimethyl-4-hydroxy-5-(p-toluamido)-pyrimidine (3.99 g, 15.5 mmol). The precipitate that formed upon acidification with HCl (conc.) was collected by filtration and dried in a vacuum oven overnight to give 0.60 g (16%) of the title compound as a tan solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 2.30 (s, 3), 2.33 (s, 3), 6.69 (s, 1), 7.24 (d, 2, J = 7.8), 7.81 (d, 2, J = 7.9), 11.79 (br s, 1), 12.18 (br s, 1). MS m/z: 240 (M+1), 238 (M-1). This material was used without further purification.



(d) 4-Chloro-2-methyl-6-(4-methylphenyl)pyrrolo[3,2-d]pyrimidine.

A mixture of 2-methyl-6-(4-methylphenyl)pyrrolo[3,2-d]pyrimidin-4-ol (0.565 g, 2.36 mmol) and POCl₃ (5.5 mL, 59.0 mmol) was heated at 120 °C for 21 h.

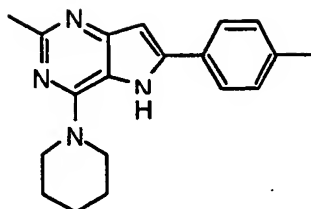
POCl₃ was removed under reduced pressure to give a dark-red residue. The residue was diluted with ice-water and neutralized under stirring and cooling with ammonia water to pH 8 (pH paper). The resulting mixture was
5 extracted three times with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo to give a brown solid. The solid was dried in vacuum oven overnight to give 0.392 g (64%) of the title compound. ¹H NMR (CDCl₃; 500 MHz): δ
10 2.43 (s, 3), 2.78 (s, 3), 6.87 (s, 1), 7.32 (d, 2, J = 7.89), 7.64 (d, 2, J = 7.99), 8.72 (br s, 1). MS m/z: 240 (base), 256 (M-1). This material was used without further purification.



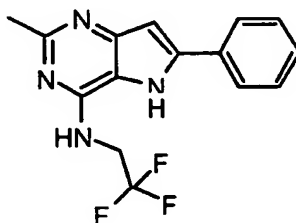
15 **(e) Diethyl[2-methyl-6-(4-methylphenyl)pyrrolo[2,3-e]pyrimidin-4-yl]amine.**

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-(4-methylphenyl)pyrrolo[3,2-d]pyrimidine (70 mg,
20 0.272 mmol), diethylamine (Aldrich Chemical Company) (0.14 mL, 1.36 mmol), and K₂CO₃ (0.376 g, 2.72 mmol) in H₂O (2.5 mL). The crude solid was purified by flash chromatography on silica gel with 20:1 CHCl₃:MeOH as eluant to give 12.1 mg (15%) of the title compound as
25 an off-white solid. ¹H NMR (CDCl₃; 500 MHz): δ 1.37 (t, 6, J = 7.0), 2.40 (s, 3), 2.56 (s, 3), 3.77 (q, 4, J = 6.7, 7.0), 6.69 (s, 1), 7.24 (d, 2, J = 7.8), 7.51 (d, 2, J = 7.7). MS m/z: 295.5 (M+1), 293.0 (M-1). HRMS: Calcd for M+H: 295.1559. Found: 295.1559.

70

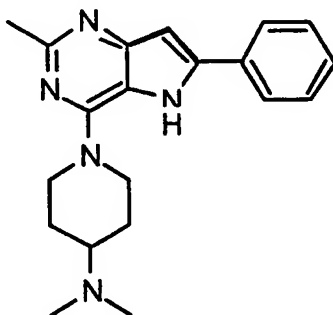
**Example 13****2-Methyl-6-(4-methylphenyl)-4-piperidylpyrrolo[3,2-d]pyrimidine.**

5 This compound was prepared according to the method described in Example 2 by employing 2-methyl-4-chloro-6-(*p*-tolyl)-5H-pyrrolo[3,2-d]pyrimidine (Example 12(d)) (70 mg, 0.272 mmol), piperidine (Aldrich Chemical Company) (0.13 mL, 1.36 mmol), and K₂CO₃ (0.376 g, 2.72 mmol) in H₂O (2.5 mL). The crude material was purified by flash chromatography on silica gel with 9:1 CHCl₃:MeOH as eluant to give 50.2 mg (60%) of the title compound as a tan solid. ¹H NMR (CDCl₃; 500 MHz): δ 1.74-1.76 (m, 6), 2.40 (s, 3), 2.58 (s, 3), 3.79-3.81 (m, 4), 6.67 (s, 1), 7.25 (d, 2, *J* = 7.8), 7.54 (d, 2, *J* = 7.7). MS *m/z*: 307 (M+1), 305 (M-1). HRMS: Calcd for M+H: 307.1923. Found: 307.1910.

**Example 14****(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(2,2,2-trifluoroethyl) amine.**

20 To a mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (55.9 mg, 0.23 mmol) and 2,2,2-trifluoroethylamine (Aldrich Chemical Company) (95 μL, 1.15 mmol) was added a solution of

K_2CO_3 (0.13 g, 0.92 mmol) in H_2O (1.5 mL). This mixture was stirred at 140 °C in a closed-capped Wheaton vial for 2.5 h. After cooling, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. The organic solution was removed and
5 the aqueous solution was washed with CH_2Cl_2 (10 mL). The combined organic solutions were washed with saturated aqueous NaCl (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was washed with CH_2Cl_2 , until all the color was
10 removed. The remaining solid was recrystallized from hot MeOH to provide 21 mg (29%) of the title compound as a white solid. Mp: >310 °C. MS m/z 307 (M+1), 294, 281, 226. 1H NMR ($DMSO-d_6$; 400 MHz): δ 2.31 (s, 3), 2.52 (s, 2), 6.74 (s, 1), 7.33 (t, 1, $J = 7.3$), 7.43
15 (t, 2, $J = 7.8$), 7.92 (d, 2, $J = 7.3$), 11.74 (s, 1), 12.22 (s, 1). HRMS: Calcd for M+H, $C_{15}H_{13}F_3N_4$: 307.1168. Found: 307.1160.



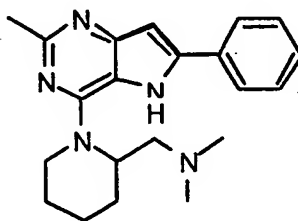
20

Example 15

Dimethyl[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(4-piperidyl)]amine.

To a mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (96.7 mg, 0.40 mmol) and 4-dimethylamine piperidine (Salor
25 Chemical Company) (0.25 g, 1.90 mmol) was added a solution of K_2CO_3 (0.35 g, 1.60 mmol) in H_2O (2.5 mL). This mixture was stirred at 140 °C in a closed-capped Wheaton vial for 1 h. After cooling the precipitate was

collected, washed with H₂O (5 x 2 mL), ether (5 x 3 mL) and dried under vacuum to give a cream-colored solid. This material was recrystallized from MeOH/CH₂Cl₂ to give 59 mg (44%) of the title compound. Mp: 261.5-263 °C. MS m/z: 336 (M+1), 291, 237. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.50 (br q, 2H, J = 10.4), 1.86 (d, 2, J = 11.8), 2.20 (s, 6), 2.42 (s, 3), 3.00 (br t, 1, J = 11.2), 4.46 (br d, 2H, J = 10.4), 6.76 (s, 1), 7.40 (br d, 1, J = 6.4), 7.47 (t, 2, J = 6.4), 7.90 (d, 2H, J = 7.6), 11.02 (s, 1). Anal. Calcd for C₂₀H₂₅N₅•H₂O: C, 67.99; H, 7.65; N, 19.83. Found: C, 67.81; H, 7.67; N, 19.75.



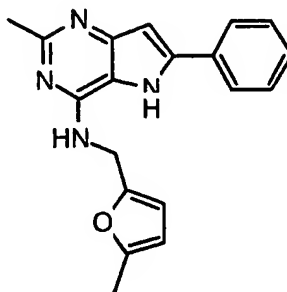
15

Example 16

Dimethyl{[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(2-piperidyl)]methyl}amine.

To a mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (88.3 mg, 0.36 mmol) and N-(2-piperidylmethyl)-dimethylamine (Salor Chemical Company) (0.25 g, 1.72 mmol) was added a solution of K₂CO₃ (0.25 g, 1.60 mmol) in H₂O (2.5 mL). This mixture was stirred at 140 °C in a closed-capped Wheaton vial for 2.5 h. After cooling, CH₂Cl₂ (10 mL) and H₂O (10 mL) were added. The organic solution was removed and the aqueous solution was washed with CH₂Cl₂ (10 mL). The combined organic solutions were washed with saturated NaCl (15 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3% MeOH:CHCl₃ on silica gel) to give 43 mg (34%) of the title compound

as a yellow oil. MS m/z : 350 (M+1), 305, 214. ^1H NMR (DMSO- d_6 ; 400 MHz): δ 1.63 (m, 6), 2.29 (s, 6), 2.40 (s, 3), 2.81 (m, 2), 3.03 (br t, 1, $J = 11.8$), 4.53-4.63 (m, 2), 6.75 (s, 1), 7.37 (m, 1), 7.50 (t, 2, $J =$
5 7.5), 7.81 (d, 2, $J = 7.8$), 12.47 (s; 1).

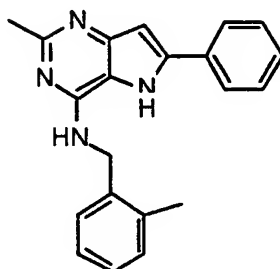


Example 17

10 **[(5-methyl(2-furyl)methyl)(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amine.**

To a mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (47.6 mg, 0.19 mmol) and 5-methyl-2-furanmethanamine (Acros Chemical Company) (100 μL , 0.98 mmol) was added a
15 solution of K_2CO_3 (0.11 g, 0.76 mmol) in H_2O (1.5 mL). This mixture was stirred at 140 $^\circ\text{C}$ in a closed-capped Wheaton vial for 2.5 h. After cooling, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. The organic solution was removed and the aqueous solution washed with CH_2Cl_2 (10
20 mL). The combined organic solutions were washed with saturated NaCl (15 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3% MeOH: CHCl_3 on silica gel) to give 37 mg (62%) of the title compound
25 as a beige solid. Mp: 125-127.5 $^\circ\text{C}$. MS m/z : 319 (M+1), 294, 225, 195, 147. ^1H NMR (CD_3OD , 400 MHz): δ 2.28 (s, 3), 2.53 (s, 3), 4.72 (s, 2), 5.97 (d, 1, $J = 3.0$), 6.24 (d, 1, $J = 3.0$), 6.66 (s, 1), 7.34 (m, 1), 7.43 (t, 2, $J = 7.7$), 7.71 (dd, 2, $J = 7.1, 1.4$).

HRMS: Calcd for M+H, C₁₉H₁₈ON₄: 319.1555. Found: 319.1566.

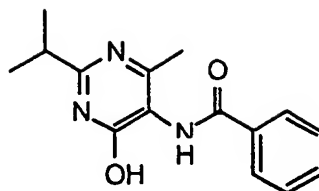


5

Example 18

[(2-methylphenyl)methyl](2-methyl-6-phenylpyrrolo[3,2-d]pyrimidin-4-yl)amine.

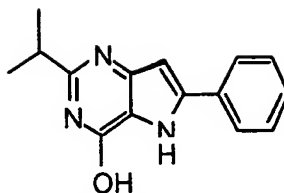
To a mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (85.0 mg, 0.35 mmol) and 2-methylbenzyl amine (Aldrich Chemical Company) (2.2 mL, 17.4 mmol) was added a solution of K₂CO₃ (0.35 g, 2.54 mmol) in H₂O (2.5 mL). This mixture was stirred at 140 °C in a closed-capped Wheaton vial for 1.5 h. After cooling, CH₂Cl₂ (10 mL) and H₂O (10 mL) were added. The organic solution was removed and the aqueous solution washed with CH₂Cl₂ (10 mL). The combined organic solutions were washed with saturated NaCl (15 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3% MeOH:CHCl₃ on silica gel) and then recrystallized from MeOH/CH₂Cl₂ to give 42 mg (35%) of the title compound as a white solid. Mp: 277-281 °C. MS m/z: 329 (M+1). ¹H NMR (DMSO-d₆; 400 MHz): δ 2.38 (s, 3), 2.42 (s, 3), 4.69 (d, 2, J = 4.8), 6.75 (s, 1), 6.98 (br t, 1), 7.19-7.25 (m, 3), 7.35-7.42 (m, 2), 7.49 (t, 2, J = 7.8), 7.76 (d, 2, J = 7.8), 11.27 (s, 1). Anal. Calcd for C₂₁H₂₀N₄: C, 76.83; H, 6.10; N, 17.07. Found: C, 76.58; H, 6.20; N, 16.94.

**Example 19****(a) 2-Isopropyl-6-methyl-4-hydroxy-5-benzamido-pyrimidine.**

To a solution of sodium ethoxide (Aldrich Chemical Company) (3.30 g, 0.046 mol) in absolute ethanol (70 mL) was added isopropylcarbamidine hydrochloride (Maybridge Chemical Company) (2.70 g, 0.022 mol).

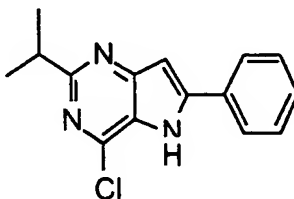
After stirring at 25 °C for 0.5 h this slurry was filtered through a plug of celite into a solution of 2-benzoylamino-3-oxo-butyric acid ethyl ester (Example 1 (b)) (5.01 g, 0.020 mol) in absolute EtOH (50 mL). The reaction mixture was placed under a N₂ atmosphere and allowed to stir at room temperature overnight. HCl (conc.) was added to acidify the solution to a pH of 4-5 (pH paper). The solids which precipitated out of solution were removed by filtration and the filtrate was concentrated under reduced pressure to give a gummy brown solid. This material was purified by recrystallization from acetone to give 1.6 g (29%) of the title compound as a white solid. Mp: 252.5-254 °C.

¹H NMR (DMSO-d₆; 500 MHz): δ 1.21 (d, 6, J = 6.9), 2.12 (s, 3), 2.83 (septet, 1, J = 6.9), 7.52 (t, 2, J = 7.6), 7.59 (t, 1, J = 7.4), 7.97 (d, 2, J = 7.4), 9.56 (s, 1), 12.51 (s, 1). MS m/z : 272 (M+1). HRMS: Calcd for M+Na, C₁₅H₁₇ON₄: 319.1555. Found: 319.1566.



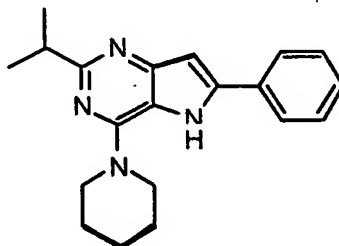
(b) 2-Isopropyl-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol.

KOt-Bu (Aldrich Chemical Company) (2.5 g, 23.0 mmol) was added portionwise at room temperature to a
5 slurry of 2-isopropyl-6-methyl-4-hydroxy-5-benzamidopyrimidine (0.62 g, 2.30 mmol) in *t*-BuOH (60 mL) in a round-bottomed flask equipped with a distillation head. The mixture was slowly heated to 180 °C under a slow stream of nitrogen until all the
10 solvent was distilled off. The temperature was slowly increased with gas evolution until the solid cake had melted at 280 °C. The temperature was kept at 280 °C for 10 min then raised to 300 °C for 10 min. The sand bath was removed allowing the reaction mixture to cool
15 to room temperature. Distilled water (100 mL) was added and HCl (conc.) was added until the pH of the solution was 4-5 (pH paper). The resulting precipitate was collected by filtration and washed with H₂O (3 x 10 mL). This material was purified by flash
20 chromatography on silica gel with 98:2 CHCl₃:MeOH as eluant to give 97 mg (17%) of the title compound as a beige solid. Mp: >300 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.23 (d, 6, *J* = 6.76), 2.88 (septet, 1, *J* = 6.78), 6.81 (s, 1), 7.33 (t, 1, *J* = 7.1), 7.44 (7.57), 7.92 (d, 2, *J* = 7.8), 11.70 (s, 1), 12.26 (s, 1). MS *m/z* : 254 (M+1). Anal. Calcd for C₁₅H₁₅N₃O: C, 71.15; H, 5.93; N, 16.61. Found: C, 70.90; H, 5.95; N, 16.53.



(c) 4-Chloro-2-isopropyl-6-phenylpyrrolo[3,2-d]pyrimidine.

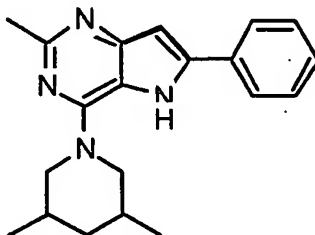
Phosphorus oxychloride (Aldrich Chemical Company) (3.0 mL, 30.0 mmol) and 2-isopropyl-4-hydroxy-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol (97.0 mg, 0.38 mmol) were added to a round-bottomed flask. The resulting mixture was heated at reflux overnight under N₂. After cooling the phosphorus oxychloride was removed under reduced pressure to provide a brown oil. This material was purified by flash chromatography on silica gel with 99:1 CHCl₃:MeOH as eluant to give 47 mg (46%) of the title compound as an off-white powder. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.31 (d, 6, J = 6.9), 3.19 (septet, 1, J = 6.8), 7.18 (s, 1), 7.47-7.57 (m, 3), 8.10 (d, 2, J = 7.4), 12.53 (s, 1). MS m/z : 272 (M+1). HRMS Calcd for M+H, C₁₅H₁₄N₃Cl: 272.0951. Found: 272.0955.



(d) 2-Isopropyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine.

To a mixture of 4-chloro-2-isopropyl-6-phenylpyrrolo[3,2-d]pyrimidine (46.0 mg, 0.17 mmol) and piperidine (Aldrich Chemical Company) (85 μL, 0.85 mmol) was added a solution of K₂CO₃ (0.10 g, 0.70 mmol) in H₂O (1.0 mL). This mixture was stirred at 140 °C in a closed-capped Wheaton vial for 1 h. After cooling, the white precipitate was collected, washed with H₂O (5 x 2 mL), ether (5 x 3 mL) and dried under vacuum to give 48 mg (88%) of the title compound as a cream colored solid. Mp: 269.5-272 °C. MS m/z : 321 (M+1), 307, 240, 171. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.25 (d, 6, J =

6.8), 1.66 (br s, 6), 2.95 (septet, 1, $J = 6.8$), 3.73 (br s, 4), 6.78 (s, 1), 7.39 (m, 1), 7.48 (m, 2), 7.89 (d, 2, $J = 7.7$), 11.06 (s, 1). Anal. Calcd for $C_{20}H_{24}N_4 \cdot 0.5H_2O$: C, 72.90; H, 7.65; N, 17.01. Found: C, 72.78; H, 7.26; N, 16.98.



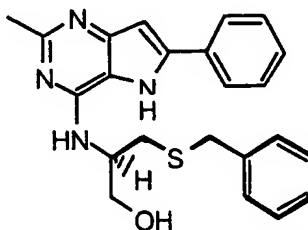
Example 20

cis/trans-4-(3,5-dimethylpiperidinyl)-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine.

To a mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (83.8 mg, 0.34 mmol) and 3,5-dimethylpiperidine (cis/trans, Aldrich Chemical Company) (250 μ L, 1.72 mmol) was added a solution of K_2CO_3 (0.19 g, 1.36 mmol) in H_2O (2.0 mL). This mixture was stirred at 140 $^{\circ}C$ in a closed-capped Wheaton vial for 2.0 h. After cooling, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. The organic solution was removed and the aqueous solution washed with CH_2Cl_2 (10 mL). The combined organic solutions were washed with saturated NaCl (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3% MeOH: $CHCl_3$ on silica gel) and then recrystallized from MeOH/ CH_2Cl_2 to give 85 mg (78%) as a beige colored solid. This material was recrystallized from hot MeOH/ CH_2Cl_2 to give 54 mg (50%) of the title compound as a 95:5 mixture of isomers as colorless crystals. Mp: 225.5–227 $^{\circ}C$. MS m/z : 321 (M+1). 1H NMR (DMSO- d_6 ; 400 MHz) (for major isomer): δ 0.90 (m, 2), 0.91 (d, 6, $J = 6.5$), 1.73 (m, 2), 2.40 (s, 3), 2.42 (br s, 2), 4.42 (br d, 1, $J =$

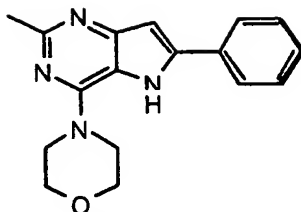
8.2), 6.74 (s, 1), 7.40 (m, 1), 7.49 (br s, 2), 7.89 (d, 2, $J = 7.4$), 11.06 (s, 1). Anal. Calcd for $C_{20}H_{24}N_4$: C, 75.00; H, 7.50; N, 17.50. Found: C, 74.87; H, 7.56; N, 17.38.

5

**Example 21**

(S)-2-[(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amino]-3-(phenylmethylthio)butan-1-ol.

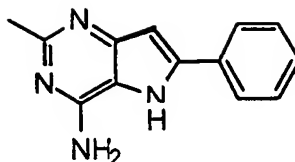
10 To a mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (78.1 mg, 0.32 mmol) and S-benzyl-1-cysteinol (Aldrich Chemical Company) (0.32 g, 1.60 mmol) was added a solution of K_2CO_3 (0.35 g, 2.54 mmol) in H_2O (2.5 mL). This mixture
15 was stirred at 140 °C in a closed-capped Wheaton vial for 2.5 h. After cooling, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added. The organic solution was removed and the aqueous solution washed with CH_2Cl_2 (10 mL). The combined organic solutions were washed with saturated
20 NaCl (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (3% MeOH: $CHCl_3$ on silica gel) to give 51 mg (40%) of the title compound as a white solid. Mp: 220-221.5 °C. MS m/z : 405
25 (M+1), 336, 203, 134. 1H NMR ($DMSO-d_6$; 400 MHz): δ 2.41 (s, 3), 2.65 - 2.78 (m, 3), 3.63 (m, 1), 3.75 (m, 1), 3.86 (s, 2), 4.52 (br s, 1), 5.12 (br s, 1), 6.75 (d, 1, $J = 1.6$), 6.99 (br d, 1, $J = 7.7$), 7.20-7.40 (m, 6), 7.50 (t, 2, $J = 7.5$), 7.82 (d, 2, $J = 7.5$), 11.53 (s, 1). Anal. Calcd for $C_{23}H_{24}N_4OS \cdot H_2O$: C, 65.40; H, 6.16; N, 13.27. Found: C, 65.05; H, 5.87; N, 13.07.
30

**Example 22**

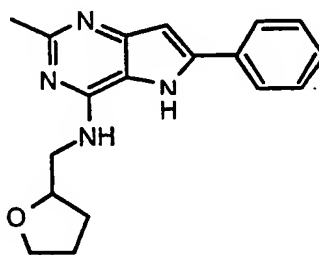
4-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)morpholine.

To a 5 mL Wheaton vial was added was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (100 mg, 0.41 mmol) and morpholine (Aldrich Chemical Company) (0.18 mL, 2.1 mmol). A solution of K_2CO_3 (0.37 g, 2.7 mmol) in H_2O (2.5 mL) was added, the vial was securely capped, and the reaction mixture was heated at 120 °C for 2 h. The reaction mixture was allowed to cool to room temperature and the resulting light-pink precipitate was collected by filtration, recrystallized from EtOAc and dried overnight in a 60 °C vacuum oven to give 0.04 g (33%) of the title compound as a white solid. Mp: 276 °C (dec.) 1H NMR ($CDCl_3$; 500 MHz): δ 2.62 (s, 3), 3.87 (s, 4), 3.90 (s, 4), 6.79 (s, 1), 7.41 (t, 1, J = 6.8), 7.48 (t, 2, J = 7.4), 7.67 (d, 2, J = 6.8), 8.17 (br s, 1). MS m/z : 295 (M+1). Anal. Calcd for $C_{17}H_{18}N_4O \cdot 0.25 H_2O$: C 68.32, H 6.24, N 18.75. Found: C 67.90, H 6.02, N 18.64.

81

**Example 23****2-Methyl-6-phenylpyrrolo[3,2-d]pyrimidin-4-ylamine.**

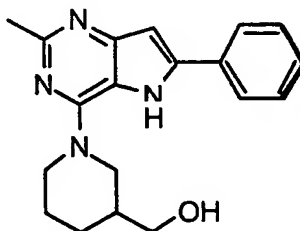
This compound was prepared according to the method described in Example 26 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (0.10 g, 0.41 mmol) with NH_4OH (Aldrich Chemical Company) (2.5 mL, 21.4 mmol) and K_2CO_3 (0.33 g, 2.4 mmol). The crude reaction mixture was concentrated to dryness and the residue extracted with hot MeOH and concentrated. The resulting yellow oil was purified by flash chromatography on silica gel (1:40 MeOH/ CH_2Cl_2 , followed by 1:20 MeOH/ CH_2Cl_2) to give 0.005 g (5%) of the title compound as an off-white solid. Mp: $>280^\circ\text{C}$. ^1H NMR (CD_3OD ; 500 MHz): δ 2.53 (s, 3), 6.74 (s, 1), 7.44 (t, 1, $J = 7.2$), 7.52 (t, 2, $J = 7.5$), 7.82 (d, 2, $J = 7.5$); MS m/z : 225 ($M+1$).

**Example 24****(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(2-perhydrofurylmethyl)amine.**

This compound was prepared according to the method described in Example 26 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (0.10 g, 0.41 mmol), tetrahydrofurfuryl amine (Aldrich Chemical Company) (0.212 mL, 2.05 mmol) and K_2CO_3 (0.34 g, 2.50 mmol) in H_2O (2.5 mL) to obtain crude pink

solids. Recrystallization from EtOH/MeOH gave 0.044g (35%) of the title compound as an off-white solid. Mp: 280 °C. ¹H NMR (CDCl₃; 500 MHz): δ 1.59 (m, 1), 1.87 (m, 2), 2.00 (m, 1), 2.39 (s, 3), 3.48 (m, 1), 3.71 (m, 2), 3.86 (t, 1, J = 7.3), 4.06 (m, 1), 6.74 (s, 1), 6.95 (s, 1), 7.38 (t, 1, J = 7.1), 7.51 (t, 2, J = 7.6), 7.80 (d, 2, J = 8.0), 11.41 (s, 1). MS m/z: 309 (M+1). Anal. Calcd for C₁₈H₂₀N₄O: C 70.11, H 6.54, N 18.17. Found: C 69.88, H 6.51, N 18.03.

10

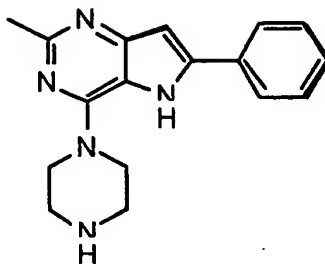
**Example 25**

[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-3-piperidyl]methan-1-ol.

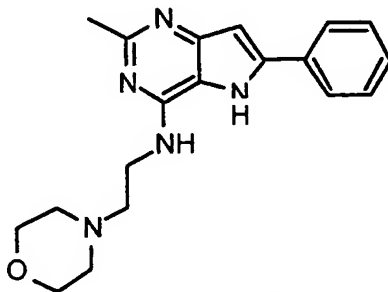
15 This compound was prepared according to the method described in Example 26 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (0.10 g, 0.41 mmol), 3-piperidinemethanol (Aldrich Chemical Company) (0.241 g, 2.09 mmol) and K₂CO₃ (0.34 g, 2.50 mmol) in H₂O (2.5 mL) to obtain crude pink solids. Recrystallization from EtOH/MeOH gave 0.040g (30%) of the title compound as an off-white solid. Mp: 255-256 °C. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.45 (m, 1), 1.59 (m, 1), 1.67 (m, 1), 1.83 (m, 2), 2.42 (s, 3), 3.47 (m, 2), 3.55 (m, 1), 3.68 (m, 2), 3.86 (m, 1), 5.44 (br s, 1), 6.77 (s, 1), 7.38 (m, 1), 7.47 (m, 2), 7.87 (d, 2, J = 7.2), 11.24 (br s, 1). MS m/z: 321 (M-1).

25

83

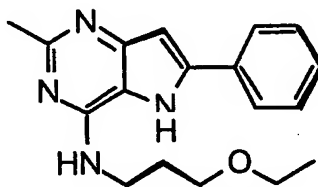
**Example 26****2-Methyl-6-phenyl-4-piperazinylnpyrrolo[3,2-d]pyrimidine.**

5 This compound was prepared according to the method described in Example 26 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (0.10 g, 0.41 mmol), piperazine (Aldrich Chemical Company) (0.382 g, 4.43 mmol) and K_2CO_3 (0.34 g, 2.50 mmol) in
10 H_2O (2.5 mL) to give crude pink solids. These solids were taken up in hot EtOAc, cooled to room temperature, and the impurities were removed by filtration. The filtrate was concentrated to give 0.035g (29%) of the title compound as an off-white solid. Mp: 236 °C. 1H
15 NMR (DMSO- d_6 ; 500 MHz): δ 2.42 (s, 3), 2.85 (t, 4, J = 5.2), 3.62 (t, 4, J = 5.2), 6.77 (s, 1), 7.36 (m, 1), 7.45 (t, 2, J = 7.8), 7.95 (d, 2, J = 7.6), 10.96 (s, 1); MS m/z : 294 (M+1). Anal. Calcd for $C_{17}H_{19}N_5O \cdot 0.5 H_2O$: C 67.53, H 6.67, N 23.16. Found: C 67.35, H 6.59, N
20 23.01.

**Example 27**

(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(2-morpholin-4-ylethyl)amine.
25

This compound was prepared according to the method described in Example 26 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (0.10 g, 0.41 mmol), 4-(2-aminoethyl)morpholine (Aldrich Chemical Company) (0.270 g, 2.06 mmol) and K_2CO_3 (0.36 g, 2.60 mmol) in H_2O (2.5 mL) to give crude pink solids. Recrystallization from EtOAc/MeOH gave 0.060g (43%) of the title compound as a white solid. Mp: >280 °C. 1H NMR (DMSO- d_6 ; 500 MHz): δ 2.39 (s, 3), 3.61 (t, 4, $J = 4.5$), 3.65 (q, 2, $J = 6.1$), 4.04 (s, 2), 6.75 (s, 1), 6.81 (br s, 1), 7.38 (t, 1, $J = 7.4$), 7.51 (t, 2, $J = 7.6$), 7.78 (d, 2, $J = 7.6$), 11.39 (s, 1). ^{13}C NMR (CD_3OD , 100 MHz): δ 26.3, 39.2, 55.9, 60.1, 68.8, 99.9, 127.3, 128.3, 130.6, 131.2, 134.0, 143.1, 149.8, 151.1, 161.5. MS m/z : 338 (M+1). Anal. Calcd for $C_{19}H_{23}N_5O \cdot 0.25H_2O$: C, 66.74; H, 6.93; N, 20.48. Found: C, 66.84; H, 6.83; N, 20.39.

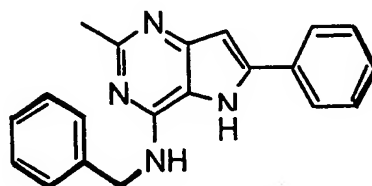


Example 28

(3-Ethoxypropyl)(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amine.

This compound was prepared according to the method described in Example 26 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (0.10 g, 0.41 mmol) with 3-ethoxypropylamine (Aldrich Chemical Company) (0.225 g, 2.18 mmol) and K_2CO_3 (0.34 g, 2.50 mmol) in H_2O (2.5 mL) to give a biphasic reaction mixture, which was partitioned between CH_2Cl_2 and H_2O . The organic layers were separated, dried over $MgSO_4$ and concentrated. The resulting yellow oil was purified by flash chromatography on silica gel (1:40

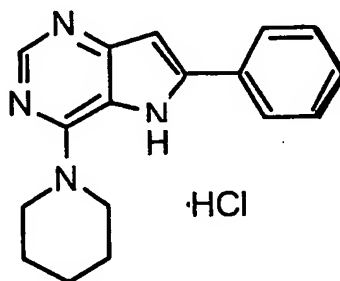
MeOH/CH₂Cl₂, followed by 1:20 MeOH/CH₂Cl₂, as eluant) to give 0.056g (44%) of the title compound as a light yellow oil that solidified upon standing. Mp: 208-209.5 °C. ¹H NMR (CDCl₃; 500 MHz): δ 1.16 (t, 3, J = 7.0), 1.99 (quin, 2, J = 5.8, 6.4), 2.58 (s, 3), 3.52 (q, 2, J = 7.1), 3.63 (t, 2, J = 5.6), 3.74 (t, 2, J = 6.6), 5.95 (br s, 1), 6.67 (s, 1), 7.33 (t, 1, J = 7.4), 7.40 (t, 2, J = 7.6), 7.66 (d, 2, J = 7.6); MS m/z: 311 (M+1).



Example 29

(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)benzylamine.

This compound was prepared according to the method described in Example 26 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (0.20 g, 0.82 mmol), benzylamine (Aldrich Chemical Company) (0.45 mL, 4.11 mmol) and K₂CO₃ (0.71 g, 5.10 mmol) in H₂O (5 mL) to obtain 0.24 g (93%) of the title compound as an off-white solid. Mp: 275-276.5 °C. ¹H NMR (DMSO-d₆, 500 MHz): δ 2.41 (s, 3), 4.73 (s, 2), 6.75 (s, 1), 7.30-7.49 (m, 9), 7.80 (d, 2, J = 7.3), 11.50 (br s, 1); MS m/z: 315 (M+1).

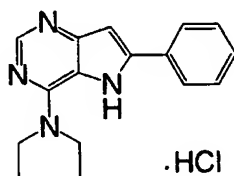


Example 30

6-Phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.

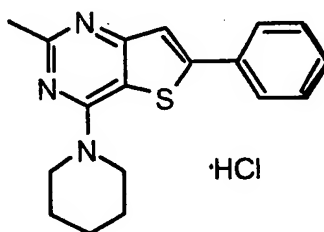
To a mixture of 1-(*N*-pyrrolyl)-1-phenyl ethylene
5 (1.54 g, 8.90 mmol) [freshly prepared through TiCl_4 mediated condensation between acetophenone (Aldrich Chemical Company) and pyrrolidine (Aldrich Chemical Company) (1.70 g, 8.76 mmol) in ether by the method described by Boger, D. L.; Duff, S. R.; Panek, J. S.;
10 Yasuda, M. *J. Org. Chem.* 1985, 50, 5782-5789)] and *N,N*-diisopropylethylamine (1.60 mL, 9.10 mmol) in toluene (15 mL) at room temperature was added 4,6-dichloro-5-nitro pyrimidine (Aldrich Chemical Company) (1.70 g, 8.76 mmol) slowly under a stream of N_2 . The reaction
15 mixture became hot upon mixing and was stirred at room temperature for 2.5 h. The solution was filtered through a fritted-funnel and the residue was washed with hot toluene (3x). The filtrate was concentrated in vacuo and the residue was dissolved in 1:2
20 toluene:dioxane (8.0-16.0 mL). Piperidine (Aldrich Chemical Company) (2.0 mL, 20 mmol) and Et_3N (2.0 mL) were slowly added (exothermic reaction). The mixture was stirred at 100 °C (sand bath temperature) for 1 h and cooled under a N_2 stream. To this solution was
25 added SnCl_4 (32 mL of a 1.5 M solution in DMF) and the mixture was stirred at room temperature overnight. The reaction mixture was poured into a mixture of NaOH (3.80 g, 95.0 mmol) and ice (~100 mL) and stirred vigorously for 30 min. The resulting slurry (pH ~9)
30 was filtered through a pad of celite, and the residue was washed exhaustively with 10:1 EtOAc:MeOH. The clear filtrate was separated and the organic phase was washed with H_2O (4 x), saturated aqueous NaCl, dried over Na_2SO_4 , filtered, and concentrated with a rotary
35 evaporator. The residue was purified by flash chromatography on silica gel with a gradient eluant of

0.4:99.6 *i*-PrOH:CH₂Cl₂, to 5:95 *i*-PrOH:CH₂Cl₂, to afford 0.73g (30%) of the title compound as a brown solid. A portion of this material was converted to it's corresponding HCl salt by treating a solution of the
5 free base in CH₂Cl₂ with 1N ethereal HCl. The resulting solid was filtered and washed with hot EtOAc. MS *m/z*⁺: 279 (M+1); *m/z*⁻: 277 (M-1). ¹H NMR (CD₃OD; 500 MHz): δ 2.12 (br s, 6), 4.53 (br s, 4), 8.01 (m, 2), 7.52 (s, 1), 7.85 (m, 3), 8.56 (s, 1). HRMS: Calcd for M+H,
10 C₁₇H₁₉N₄: 279.1606. Found: 279.1606

**Example 31****Diethyl(6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amine****15 Hydrochloride.**

To a mixture of 1-(*N*-pyrrolyl)-1-phenyl ethylene (2.0 g, 11.5 mmol) [freshly prepared through TiCl₄ mediated condensation between acetophenone (Aldrich Chemical Company) and pyrrolidine (Aldrich Chemical
20 Company) (1.70 g, 8.76 mmol) in ether by the method described by Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. J. *Org. Chem.* 1985, 50, 5782-5789)] and Et₃N (1.7 mL, 12.2 mmol) in CH₂Cl₂ (15 mL) at room temperature was added 4,6-dichloro-5-nitro pyrimidine
25 (Aldrich Chemical Company) (1.6 g, 8.2 mmol) slowly under a stream of N₂. The reaction mixture became hot upon mixing and the solution was stirred at room temperature for 2.5 h. The solution was concentrated and the residue was treated with hot toluene, filtered,
30 washed with hot toluene (3 x), and the filtrate was concentrated in vacuo. Half of this material was dissolved in toluene (10 mL), and Et₃N (2.0 mL)

followed by Et₃NH (Aldrich Chemical Company) (2.0 mL, 20 mmol) were added slowly, leading to an exothermic reaction. The mixture was stirred at 100 °C (sand bath temperature) overnight, cooled under a N₂ stream, and partitioned between H₂O and EtOAc. The organic layer was concentrated *in vacuo*. The residue was dissolved in *i*-PrOH-MeOH (5:1, ~20 mL) and hydrogenated with 10% Pd/C (0.5 g) and PtO₂ (0.1 g) as catalysts for 4 d at room temperature and atmospheric pressure. The solution was filtered through a plug of celite and concentrated with a rotary evaporator. The residue was purified by flash chromatography on silica gel with a gradient eluant of *i*-PrOH (0.4 to 5%):CH₂Cl₂ (99.6 to 95%) to afford the free base which was treated with 1N ethereal HCl to give 0.035 g (3.0%) of the title compound as a yellow solid. MS *m/z*⁺ 267 (M+1); *m/z*⁻ 265 (M-1). ¹H NMR (CD₃OD; 500 MHz): δ 1.46 (t, 6, *J* = 7.0), 4.26 (q, 4, *J* = 7.0), 7.61 (m, 3), 7.23 (s, 1), 8.30 (s, 1), 7.73 (m, 2). HRMS: Calcd for M+H, C₁₆H₁₅N₄: 267.1606. Found: 267.1598.

**Example 32**

2-Methyl-6-phenyl-4-piperidylthiopheno[3,2-d]pyrimidine Hydrochloride.

A mixture of methyl 3-amino-5-phenylthiophene 2-carboxylate (Maybridge) (2.4 g, 10.6 mmol), acetamidine hydrogen chloride (Aldrich Chemical Company) (1.2 g, 12.3 mmol), and NaOMe (Aldrich Chemical Company) (1.0 g, 18.5 mmol) in polyethylene glycol (Aldrich Chemical Company) (20 mL) was heated at 120 °C for 2 d. The

mixture was poured into aqueous 0.13 M HCl (50 mL, 6.4 mmol) and the resulting slurry was filtered. The solid was washed with distilled H₂O, dissolved in CH₂Cl₂, and DMF, and concentrated with a rotary evaporator.

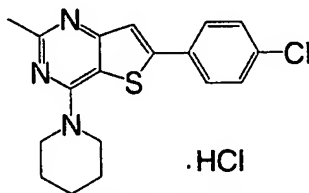
5 Toluene was added to the residue and the solution was concentrated to remove the residual H₂O (this process was repeated two additional times). To this material was added neat POCl₃ (15 mL) and the mixture was heated at 100 °C for 12 h. The solvent was evaporated in

10 vacuo, and the residue was dissolved in toluene and concentrated (this process was repeated two additional times) to remove the residual POCl₃. The residue was dissolved in toluene (15 mL) and treated with piperidine (Aldrich Chemical Company) (5 mL). The

15 mixture was heated at 100 °C for 12 h, cooled to room temperature, washed with aqueous NaHCO₃, dried over Na₂SO₄, and concentrated with a rotary evaporator. This material was purified by flash chromatography on silica gel with 1:1 EtOAc:hexanes as eluant. Treatment of the

20 free base with 1N ethereal HCl afforded 80 mg (2.2%) of the title compound as a yellow solid. MS m/z: 310 (M+1). ¹H NMR (2:1 DMSO-d₆:CD₃OD-d₄; 400 MHz): δ 1.79 (br s, 6), 2.54 (s, 3), 4.16 (br s, 4), 7.56 (m, 3), 7.73 (s, 1), 7.91 (m, 2). HRMS: Calcd for M+H, C₁₈H₂₀N₃S: 310.1374. Found: 310.1377.

25



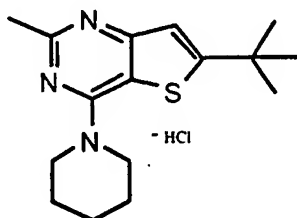
Example 33

6-(4-Chlorophenyl)-2-methyl-4-piperidylthiopheno[3,2-d]pyrimidine Hydrochloride.

30

This compound was prepared by the method described in Example 32 by using methyl 3-amino-5-(4-chloro-

phenyl)thiophene 2-carboxylate (Maybridge) (1.30 g, 4.86 mmol) to give 170 mg (10%) of the title compound as a tan solid. MS m/z : 344 (M+1), 343. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 1.75 (br s, 6), 2.62 (s, 3), 4.12 (br s, 4), 7.63 (d, 2, $J = 8.0$), 7.84 (s, 1), 7.96 (d, 2, $J = 8.5$). HRMS: Calcd for M+H, $\text{C}_{18}\text{H}_{19}\text{ClN}_3\text{S}$: 344.0984. Found: 344.0971.

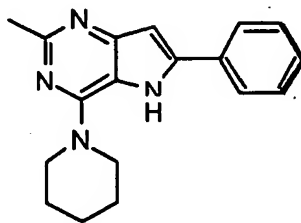


10

Example 34**6-(tert-Butyl)-2-methyl-4-piperidylthiopheno[3,2-d]pyrimidine Hydrochloride.**

This compound was prepared by the method described in Example 32 by using methyl 3-amino-5-tert-butylthiophene 2-carboxylate (Maybridge) (0.90 g, 4.22 mmol) to give 110 mg (8%) of the title compound as a white solid. MS m/z : 290.0 (M+1). ^1H NMR (DMSO- d_6 ; 500 MHz): δ 1.45 (s, 15), 2.72 (s, 3), 4.07 (br s, 4), 7.43 (s, 1). HRMS: Calcd for M+H, $\text{C}_{16}\text{H}_{22}\text{N}_3\text{S}$: 290.1686. Found: 290.1686.

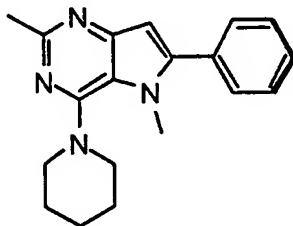
20

**Example 35****2-Methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.**

25

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-

6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (1.0 g, 4.1 mmol), piperidine (Aldrich Chemical Company) (2.0 mL, 20.52 mmol), and K_2CO_3 (2.84 g, 20.52 mmol) in H_2O (30 mL). The precipitate that formed was collected by
5 filtration, washed with water and hexane to give a brown solid as crude product. This material was purified by flash chromatography on silica gel with 2:1 EtOAc:hexanes as eluant to give 0.84 g (70%) of the free base as an off-white solid. 1H NMR ($CDCl_3$; 500
10 MHz): δ 1.74-1.76 (m, 6), 2.60 (s, 3), 3.79-3.81 (m, 4), 6.76 (s, 1), 7.38-7.49 (m, 3), 7.66 (d, 2, J = 7.54). MS m/z : 293 ($M+1$), 291 ($M-1$). A portion of this free base (450 mg, 1.54 mmol) was dissolved in minimum amount of $CHCl_3$, and HCl (1.54 mL, 1.54 mmol,
15 of a 1N solution in ether) was added dropwise. The mixture was stirred at room temperature for 20 min and the solvent was evaporated in vacuo to give a light-yellow foam. This material was recrystallized from MeOH- H_2O to give 260 mg of the title compound as white
20 needles. Mp: 293-294 $^{\circ}C$. 1H NMR ($DMSO-d_6$; 500 MHz): δ 1.71-1.72 (m, 6), 2.58 (s, 3), 4.06-4.07 (m, 4), 6.89 (s, 1), 7.50-7.57 (m, 3), 7.96 (d, 2, J = 7.1), 12.0 (br s, 1), 14.4 (br s, 1). Anal. Calcd for $C_{18}H_{21}ClN_4 \cdot H_2O$: C, 62.33; H, 6.68; Cl, 10.22; N, 16.15.
25 Found: C, 62.25; H, 6.64; N, 16.14; Cl, 10.34.

**Example 36**

2,5-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-d]
30 pyrimidine.

A suspension of 2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyridine (Example 35) (57 mg, 0.20 mmol) in THF (3 mL) was placed under a N₂ atmosphere and cooled with a dry-ice bath to -78 °C.

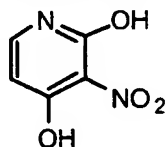
5 *n*-Butyl lithium (Aldrich Chemical Company) (360 µL, 0.90 mmol, 4.5 equiv of a 2.5 M solution in hexanes) was added slowly. The reaction mixture was stirred at -78 °C for 1 h and allowed to warm to 0 °C. Dimethyl sulfate (Eastman Kodak Company) (73.8 mg, 0.60 mmol,

10 3.0) was added slowly at 0 °C. The solution was allowed to warm to room temperature and stir overnight. The reaction was quenched by the addition of 10% NH₄Cl (3 mL) and the THF was evaporated under reduced pressure. The solution was extracted with CHCl₃ (3 x

15 50 mL), and the combined organic layers were washed with saturated NaCl, dried over Na₂SO₄, filtered and concentrated with a rotary evaporator. The crude material was purified by flash chromatography on silica gel with a gradient eluant of EtOAc(0-20%):hexanes(100-

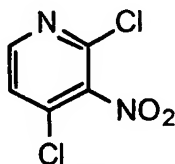
20 80%) to provide 20 mg (34%) of the title compound as a white solid [30 mg (53%) of recovered starting material was also obtained]. Mp: 131-132 °C. ¹H NMR (acetone-d₆, 400 MHz): δ 7.68 (d, 2, *J* = 7.0), 7.54 (t, 2, *J* = 7.0), 7.47 (t, 1, *J* = 7.0), 3.84 (s, 3), 3.40 (t, 4, *J* = 4.9), 2.50 (s, 3), 1.78 (m, 4), 1.70 (m, 2). MS *m/z*:

25 307 (M+1).

Example 37**30 (a) 2,4-Dihydroxy-3-nitropyridine.**

Fuming HNO₃ (40 mL) was added to a stirring solution of 2,4-dihydroxypyridine (Aldrich Chemical Company) (9.0

g, 81 mmol) in H₂SO₄ (conc.) (40 mL) at 0 °C. After 30 min, the solution was poured onto crushed ice (~80 mL) (caution: a non-violent exothermic reaction resulted), and the mixture was chilled in a freezer. The
5 resulting precipitate was filtered, washed with cold water, and dried to constant weight in vacuo to afford 11.4 g (90%) of the title compound as a colorless solid. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 6.13 (d, 1, *J* = 7.2), 7.48 (d, 1, *J* = 7.0), 11.93 (s, 1), 12.42 (br s,
10 1). MS *m/z*: 157 (*M*+1).



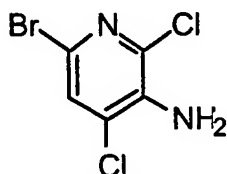
(b) 2,4-Dichloro-3-nitropyridine.

2,4-Dihydroxy-3-nitropyridine (1.56 g, 10 mmol) was taken up in POCl₃ (Aldrich Chemical Company) (20 mL)
15 and the resulting black mixture was heated at reflux for 24 h. The volume of the solution was reduced by 70 % in vacuo, and the cooled mixture was carefully poured onto crushed ice (caution: a violent exothermic reaction may result) and extracted with EtOAc (2x).
20 The combined extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was dissolved in 1:1 EtOAc:hexanes, filtered through a plug of silica gel, and concentrated in vacuo to afford 1.5 g (80%) of the title compound as a
25 colorless crystalline solid. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 8.14 (d, 1, *J* = 5.1), 8.72 (d, 1, *J* = 5.2).



(c) 3-Amino-2,4-dichloropyridine.

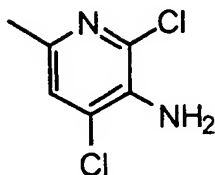
2,4-Dichloro-3-nitropyridine (1.5 g, 8 mmol) was dissolved in Et₂O (8 mL). A solution of SnCl₂·2H₂O (18 g, 80 mmol) in HCl (conc.) (18 mL) was added cautiously. The reaction was exothermic upon this addition and the Et₂O boiled off of the solution. The reaction mixture was allowed to stir overnight at room temperature. The solution was cooled to 0 °C in an ice-water bath and the precipitate was collected via filtration. The resulting solid was suspended in distilled H₂O, and the mixture was adjusted to neutral pH by the addition of concentrated NH₄OH at 0 °C. The resulting solution was extracted with EtOAc (2x). The combined extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo* to afford 1.2 g (90%) of the title compound as a colorless crystalline solid. ¹H NMR (DMSO-*d*₆; 500 MHz): δ 5.88 (s, 2) 7.35 (d, 1, *J* = 5.1), 7.63 (d, 1, *J* = 5.1). MS *m/z*: 163 (M+1).



(d) 3-Amino-6-bromo-2,4,-dichloropyridine.

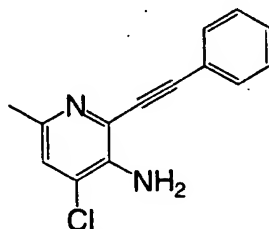
3-Amino-2,4-dichloropyridine (500 mg, 3.1 mmol) was dissolved in DMF (16 mL) and cooled to 0 °C in an ice-water bath. A solution of *N*-bromosuccinimide (660 mg, 3.7 mmol) in DMF (7 mL) was then added slowly. After 15 min, the solution was poured into H₂O and extracted with EtOAc (2x). The combined extracts were washed with H₂O and brine, dried over MgSO₄, filtered and concentrated *in vacuo* to obtain a red residue. This residue was dissolved in 1:1 EtOAc:hexanes, filtered through a plug of silica gel, and concentrated *in vacuo* to afford 0.68 g (90%) of the title compound as a

colorless crystalline solid. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 6.10 (s, 2), 7.69 (s, 1). MS m/z : 243 ($M+1$; ^{81}Br), 241 ($M+1$; ^{79}Br).



5 **(e) 3-Amino-2,4-dichloro-6-methylpyridine.**

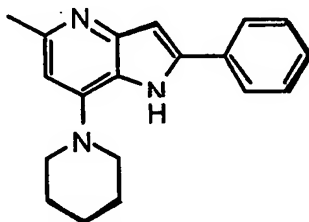
3-Amino-6-bromo-2,4,-dichloropyridine (500 mg, 2.1 mmol) was dissolved in anhydrous DMF (10 mL), and MeB(OH)_2 (Aldrich Chemical Company) (380 mg, 6.3 mmol), K_2CO_3 (1.5 g, 10 mmol), and $(\text{PPh}_3)_2\text{PdCl}_2$ (150 mg, 0.21 mmol) were added. The mixture was heated to 100 °C for 24 h, then cooled to room temperature, poured into H_2O and extracted with EtOAc (2x). The combined extracts were washed with H_2O and brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 1:4 EtOAc:hexanes to afford 0.31 g (85%) of the title compound as a colorless crystalline solid. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 2.28 (s, 3), 5.65 (s, 2), 7.34 (s, 1). MS m/z : 177 ($M+1$).



20 **(f) 3-Amino-4-chloro-6-methyl-2-(2-phenylethynyl)pyridine.**

To a solution of 3-amino-2,4-dichloro-6-methylpyridine (220 mg, 1 mmol) in NEt_3 (5 mL), was added $(\text{PPh}_3)_2\text{PdCl}_2$ (35 mg, 0.05 mmol), and CuI (9.5 mg, 0.05 mmol). The mixture was cooled to 0 °C and phenyl acetylene (160 μl , 1.5 mmol) was added. The mixture

was allowed to warm to room temperature then heated at 80 °C for 4 h. The mixture was cooled to room temperature and filtered through celite. The celite was rinsed with NEt_3 , and the filtrate was concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 1:4 EtOAc:hexanes to afford 0.22 g (90%) of the title compound as a dark brown solid. ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 2.31 (s, 3), 5.55 (br s, 2), 7.26 (s, 1), 7.44 (m, 3), 7.69 (m, 2). MS m/z : 243 ($M+1$).

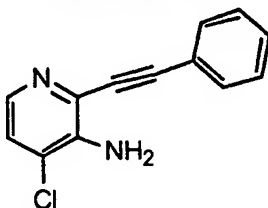


(g) 5-Methyl-2-phenyl-7-piperidylpyrrolo[3,2-b]pyridine.

Method A: 3-Amino-4-chloro-6-methyl-2-(2-phenylethynyl)pyridine (240 mg, 1 mmol) was taken up in 4:1 o-xylene/piperidine (10 mL) and heated to 140 °C in a Teflon-capped pressure tube for 7 d. The mixture was cooled to room temperature and the resulting precipitate was filtered and washed with o-xylene, followed by acetonitrile. The precipitate was dried to constant weight in vacuo to afford 0.23 g (80%) of the title compound as a pale yellow solid. ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.65 (m, 2), 1.75 (m, 4), 2.42 (s, 3), 3.32 (br s, 4), 6.49 (s, 1), 6.80 (s, 1), 7.33 (t, 1, $J = 7.2$), 7.43 (m, 2), 7.90 (d, 2, $J = 7.2$), 11.1 (br s, 1). MS m/z : 292 ($M+1$).

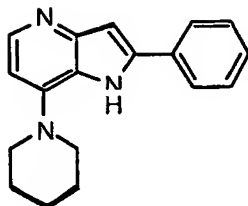
Method B: 3-Amino-4-chloro-6-methyl-2-(2-phenylethynyl)pyridine (1.24 g, 5.1 mmol) was dissolved in anhydrous DMF (90 mL), CuI (150 mg, 0.8 mmol) was added and the mixture was heated at 110 °C for 18 h. The

cooled mixture was poured into H₂O (125 mL) and extracted with EtOAc (2 x 100 mL). The combined extracts were washed with H₂O and brine, dried over MgSO₄ and filtered through a plug of silica using CHCl₃. The crude product was triturated with 20:1 hexanes:EtOAc, filtered, and dried under high vacuum to afford 600 mg (48%) of 7-chloro-5-methyl-2-phenyl pyrrolo-[3,2-b]pyridine. ¹H NMR (DMSO-d₆; 500 MHz): δ 2.40 (s, 3), 7.05 (s, 1), 7.16 (s, 1), 7.38 (t, 1, J = 5.2), 7.49 (m, 2), 8.02 (d, 2, J = 7.2). MS m/z: 243 (M+H). This intermediate chloride (273 mg, 1.1 mmol) was taken up in 4:1 o-xylene/piperidine (10 mL) and heated to 140 °C in a Teflon-capped pressure tube for 7 d. The mixture was cooled to room temperature, diluted with H₂O (125 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with H₂O and brine, dried over MgSO₄, filtered, and concentrated in vacuo. Chromatography on silica gel eluting with 10:1 CHCl₃:MeOH afforded 244 mg (75%, 36% overall) of the title compound as a pale yellow solid. The product's ¹H-NMR was identical to that obtained using Method A.

Example 38

(a) **3-Amino-4-chloro-2-(2-phenylethynyl)pyridine.** This material was prepared according to the method described in Example 37(f) starting with 3-Amino-2,4-dichloropyridine (160 mg, 1.0 mmol) to give 0.20 g (90%) of the title compound as a tan solid. ¹H NMR (DMSO-d₆; 500 MHz): δ 5.94 (s, 2), 7.39 (d, 1, J =

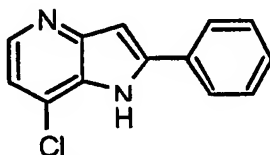
5.0), 7.54 (m, 3), 7.75 (m, 2), 7.82 (d, 1, $J = 5.0$).
MS m/z : 229 (M+1).



(b) 2-Phenyl-7-piperidylpyrrolo[3,2-b]pyridine.

5 This material was prepared according to Example 37(g) by employing 3-Amino-4-chloro-2-(2-phenylethynyl)pyridine (0.20 g 0.90 mmol). The crude material was purified by flash chromatography on silica gel with 1:9 MeOH:EtOAc as eluant to afford 0.20
10 g (80 %) of the title compound as a colorless solid. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 1.77 (m, 6), 3.32 (m, 4), 6.63 (d, 1, $J = 5.2$), 6.94 (s, 1), 7.36 (dd, 1, $J = 7.4, 7.2$), 7.53 (dd, 2, $J = 7.6, 7.8$), 7.94 (d, 2, $J = 8.1$), 8.11 (br s, 1), 11.04 (br s, 1). MS m/z : 278
15 (M+1).

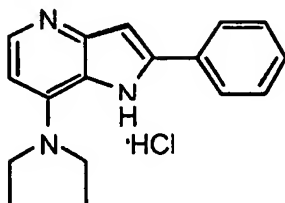
Example 39



(a) 7-Chloro-2-phenylpyrrolo[3,2-b]pyridine.

20 3-Amino-4-chloro-2-(2-phenylethynyl)pyridine (Example 38(a)) (229 mg, 1 mmol) was dissolved in anhydrous DMF (10 mL), and CuI (9.5 mg, 0.05 mmol) was added, and the mixture was heated at 100 °C for 6 h. The cooled mixture was poured into H₂O and extracted with EtOAc
25 (2x). The combined extracts were washed with H₂O and brine, dried over MgSO₄, filtered through a plug of silica gel, and concentrated in vacuo to afford 190 g (85%) of the title compound as a tan solid. ^1H NMR

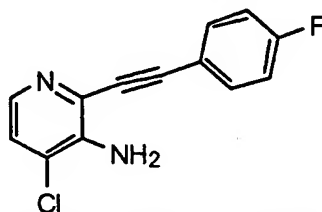
(DMSO- d_6 ; 500 MHz): δ 7.18 (s, 1), 7.30 (d, 1, $J=7.1$), 7.43 (m, 1), 7.54 (m, 2), 8.04 (d, 2, $J = 7.7$), 8.33 (d, 1, $J = 7.0$), 10.91 (s, 1). MS m/z : 229 (M+H).



5 **(b) Diethyl(2-phenylpyrrolo[3,2-b]pyridin-7-yl)amine Hydrochloride.**

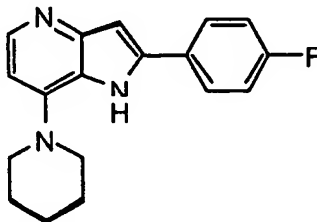
This material was prepared according to the method described in Example 37(g) by employing 7-chloro-2-phenylpyrrolo[3,2-b]pyridine (195 mg, 0.85 mmol) and
10 4:1 *o*-xylene:*N,N*-diethylamine (10 mL). This material was purified by flash chromatography on silica gel with 1:9 MeOH:EtOAc as eluant to give the free base as a tan solid. This material was dissolved in EtOAc and treated with excess 1N ethereal HCl. The resultant
15 precipitate was collected via filtration and triturated with acetonitrile to afford 180 g (80 %) of the title compound as a colorless solid. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 1.29 (t, 6, $J = 7.0$), 3.94 (q, 4, $J = 7.0$), 6.51 (d, 1, $J = 7.1$), 7.30 (s, 1), 7.55 (m, 3), 7.92
20 (m, 2), 8.14 (d, 1, $J = 7.1$), 11.30 (br s, 1). MS m/z : 266 (M+1).

Example 40



25 **(a) 3-Amino-4-chloro-2-[2-(4-fluorophenyl) ethynyl]pyridine.**

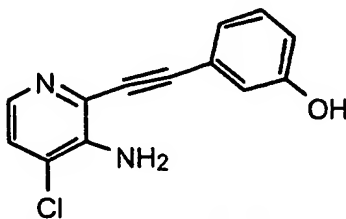
This material was prepared according to the method described in Example 37(f) by employing 3-Amino-2,4-dichloropyridine (Example 37(c)) (162 mg, 1.0 mmol) and 4-fluoroethynylbenzene (Aldrich Chemical Company) (180 mg, 1.5 mmol) to give 0.22 g (90%) of the title compound as an amber oil. MS m/z : 247 (M+1).



(b) 2-(4-Fluorophenyl)-7-piperidylpyrrolo[3,2-b]pyridine.

10 This material was prepared according to the method described in Example 37(g) by employing 3-Amino-4-chloro-2-[2-(4-fluorophenyl)ethynyl]pyridine (0.22 g, 0.90 mmol). The crude material was purified by flash chromatography with 1:9 MeOH:EtOAc) as eluant to give 0.21 g (80 %) of the title compound as an off-white solid. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 1.67 (m, 6), 3.34 (m, 4), 6.66 (d, 1, $J = 5.3$), 6.95 (s, 1), 7.31 (m, 2), 8.03 (m, 2), 8.11 (m, 1), 11.10 (br s, 1). MS m/z : 296 (M+1). Anal.

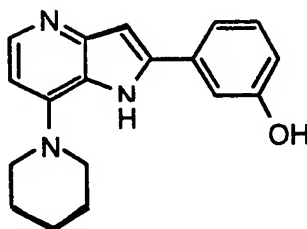
20 Calcd for $\text{C}_{18}\text{H}_{18}\text{FN}_3 \cdot 0.8\text{H}_2\text{O}$: C, 69.79; H, 6.38; N, 13.56. Found: C, 69.55; H, 6.00; N, 13.32.



Example 41

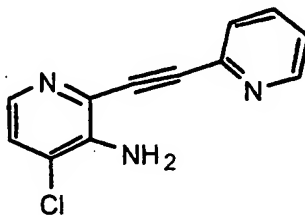
25 **(a) 3-Amino-4-chloro-2-[2-(3-hydroxyphenyl)ethynyl]pyridine.**

This material was prepared according to the method described in Example 37(f) by employing 3-Amino-2,4-dichloropyridine (Example 37(c)) (0.16 g, 1.0 mmol) and 3-hydroxyethynylbenzene (Aldrich Chemical Company) (0.15 g, 1.5 mol) to give 0.22 g (90%) of the title compound as a solid. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 5.82 (s, 2), 6.83 (m, 1), 7.00 (m, 1), 7.11 (m, 1), 7.20 (m, 1), 7.41 (m, 1), 7.83 (m, 1), 9.78 (s, 1). MS m/z : 245 (M+1).



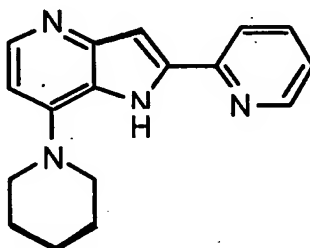
10 **(b) 2-(3-Hydroxyphenyl)-7-piperidylpyrrolo[3,2-b]pyridine.**

This material was prepared according to the method described in Example 37(g) by employing 3-Amino-4-chloro-2-[2-(3-hydroxyphenyl)ethynyl]pyridine (0.22 g, 0.90 mmol) and 4:1 o-xylene/piperidine (10 mL). The crude material was purified by flash chromatography on silica gel with 1:9 MeOH:EtOAc as eluant to give 0.18 g (70 %) of the title compound as an off-white solid. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 1.69 (m, 6), 3.31 (m, 4), 6.58 (m, 1), 6.79 (m, 2), 7.31 (m, 3), 8.09 (br s, 1), 9.55 (br s, 1), 11.01 (br s, 1). MS m/z : 294 (M+1). Anal. Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O} \cdot 0.5\text{CH}_3\text{OH}$: C, 71.82; H, 6.84; N, 13.58. Found: C, 71.99; H, 6.99; N, 13.12.



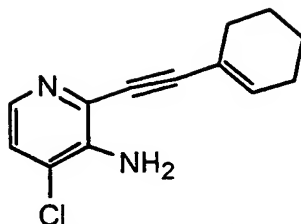
Example 42**(a) 3-Amino-4-chloro-2-[2-(2-pyridyl)ethynyl]pyridine.**

This material was prepared according to the method described in Example 37(f) by employing 3-amino-2,4-dichloropyridine (Example 37(c)) (0.16 g, 1.0 mmol) and 2-ethynylpyridine (Aldrich Chemical Company) (0.15 g, 1.5 mmol). The crude material was purified by flash chromatography on silica gel with 1:1 EtOAc:hexanes to afford 46 mg (20%) of the title compound as a tan solid. ¹H NMR (DMSO-d₆; 500 MHz): δ 5.98 (s, 2), 7.41 (d, 1, *J* = 5.0), 7.50 (m, 1), 7.63 (m, 1), 7.81 (d, 1, *J* = 5.0), 7.87 (m, 1), 8.65 (d, 1, *J* = 4.9). MS *m/z*: 230 (M+1).

**(b) 7-Piperidyl-2-(2-pyridyl)pyrrolo[3,2-b]pyridine.**

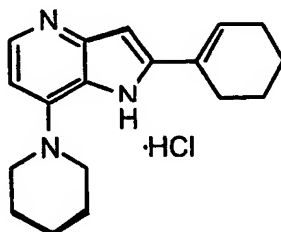
This material was prepared according to the method described in Example 37(g) by employing 3-amino-4-chloro-2-[2-(2-pyridyl)ethynyl]pyridine (46 mg, 0.20 mmol). The crude material was purified by flash chromatography on silica gel with 1:9 MeOH:EtOAc as eluant to afford 50 mg (90%) of the title compound as a tan solid. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.75 (m, 6), 3.31 (m, 4), 6.62 (m, 1), 7.19 (m, 1), 7.42 (m, 1), 7.93 (m, 1), 8.10 (m, 2), 8.68 (m, 1), 11.01 (br s, 1). MS *m/z*: 279 (M+1).

103

**Example 43**

(a) 3-Amino-4-chloro-2-[2-cyclohex-1-enylethynyl]pyridine.

- 5 This material was prepared according to the method described in Example 37(f) by employing 3-amino-2,4-dichloropyridine (Example 37(c)) (0.16 g, 1.0 mmol) and 1-ethynylcyclohexene (Aldrich Chemical Company) (0.16 g, 1.5 mol) to afford 0.23 g (99 %) of the title
- 10 compound as a viscous amber oil. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 1.63 (m, 4), 2.20 (m, 4), 5.65 (s, 2), 6.42 (m, 1), 7.27 (d, 1, $J = 5.0$), 7.71 (d, 1, $J = 5.0$). MS m/z : 233 (M+1).



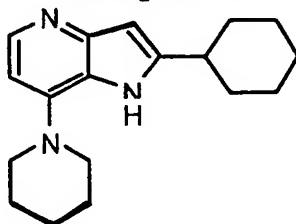
- 15 **(b) 2-Cyclohex-1-enyl-7-piperidylpyrrolo[3,2-b]pyridine Hydrochloride.**

- This material was prepared according to the method described in Example 37(g) by employing 3-Amino-4-chloro-2-[2-cyclohex-1-enylethynyl]pyridine (0.23 g, 1.0 mmol). The free base was dissolved in EtOAc and treated with excess 1N ethereal HCl. The resultant precipitate was collected via filtration and triturated with acetonitrile to afford 0.25 g (90 %) of the title
- 20 compound as an off-white solid. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 1.75 (m, 6), 2.30 (m, 4), 3.33 (m, 4), 3.71 (m, 4), 6.58 (s, 1), 6.72 (m, 1), 6.94 (d, 1, $J = 7.0$),

104

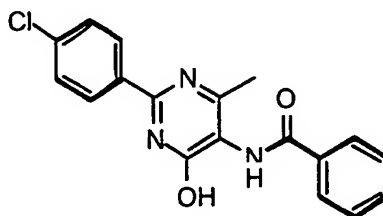
8.11 (d, 1, $J=7.0$), 11.42 (s, 1), 13.80 (br s, 1). MS m/z : 282 (M+1), 254 (M+1-28). Anal. Calcd for $C_{18}H_{23}N_3 \cdot HCl \cdot 0.75H_2O$: C, 65.25; H, 7.75; N, 12.68. Found: C, 65.38; H, 7.39; N, 12.54.

5

Example 44**2-Cyclohexyl-7-piperidylpyrrolo[3,2-b]pyridine.**

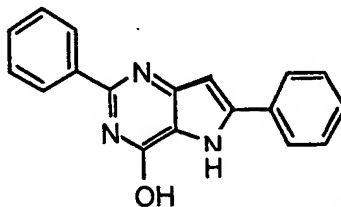
2-Cyclohex-1-enyl-7-piperidylpyrrolo[3,2-b]pyridine (Example 43(b)) (280 mg, 1 mmol) was dissolved in MeOH (5 mL), and 10% palladium on charcoal (28 mg) was added. The flask was purged with H_2 and a doubled-walled balloon filled with H_2 was attached to the flask (~30 psi H_2). After 16 h, the mixture was filtered through celite, and the filtrate was concentrated in vacuo. The crude material was purified by flash chromatography 1:9 MeOH:EtOAc to afford 0.28 g (99 %) of the title compound as an off-white solid. 1H NMR (DMSO- d_6 ; 500 MHz): δ 2.0-1.2 (m, 16), 2.72 (m, 1), 3.18 (t, 4, $J = 5.2$), 6.22 (s, 1), 6.55 (d, 1, $J = 5.3$), 8.04 (d, 1, $J = 5.3$), 10.61 (s, 1). MS m/z : 284 (M+1). Anal. Calcd for $C_{18}H_{25}N_3 \cdot 0.2H_2O$: C, 75.33; H, 8.92; N, 14.64. Found: C, 75.39; H, 8.64; N, 14.64.

25

**Example 45**

(a) 2-(4-Chlorophenyl)-4-hydroxy-6-methyl-5-benzamido-pyrimidine.

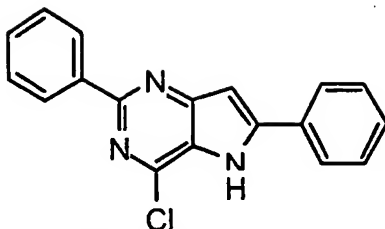
To a solution of sodium ethoxide (Aldrich Chemical Company) (7.00 g, 0.099 mol) in absolute ethanol (70 mL) was added 4-chlorobenzamidine hydrochloride (Maybridge Chemical Company) (7.50 g, 0.040 mol). After stirring at 25 °C for 0.5 h this slurry was filtered through a plug of celite into a solution of 2-benzoylamino-3-oxo-butyric acid ethyl ester (Example 1 (c)) (8.18 g, 0.033 mol). The mixture was placed under a N₂ atmosphere and allowed to stir at room temperature overnight. The precipitate was collected by filtration, washed with ethanol (3 x 20 mL) and dried under vacuum to provide 2.32 g (21%) of the title compound as a beige solid. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 2.25 (s, 3), 7.51-7.62 (m, 5), 8.00 (d, 2, J = 7.3), 8.15 (d, 2, J = 7.6), 9.68 (s, 1), 12.96 (s, 1). MS m/z : 340 (M+1), 322 (M-H₂O).



(b) 2,6-Diphenylpyrrolo[3,2-d]pyrimidin-4-ol.

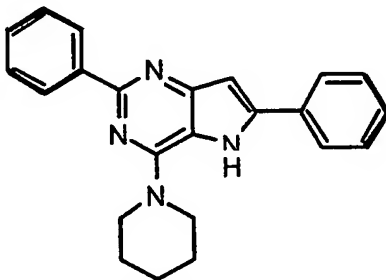
This material was prepared according to the method described in Example 1(d) by employing 2-(4-chlorophenyl)-4-hydroxy-6-methyl-5-benzamidopyrimidine (Example 45(a)) (2.03 g, 24.0 mmol). The mixture was slowly heated to 180 °C under a slow stream of nitrogen until all the solvent was distilled off. The temperature was slowly increased to 340 °C. The temperature was kept at 340 °C for 10 min then allowed to cool to room temperature. Water (50 mL) was added to the residue and HCl (conc.) was added until the pH of the solution was 4-5 (pH paper). The precipitate was collected by filtration and washed with H₂O (3 x 10

mL). This material was purified by flash chromatography on silica gel with 99:1 CHCl₃:MeOH as eluant to give 420 mg (24%) of the title compound as a beige solid (Analytical data obtained for this product indicated that the para-chloro group in the starting material was reduced under the above reaction conditions). Mp: 227-231 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 6.95 (d, 1, J = 2.1), 7.36 (t, 1, J = 7.3), 7.44-7.52 (m, 5), 7.97 (d, 2, J = 7.4), 8.11 (dd, 2, J = 5.4, 7.6), 12.12 (s, 1), 12.46 (s, 1). MS m/z : 288 (M+1).



(c) 4-Chloro-2,6-diphenylpyrrolo[3,2-d]pyrimidine.

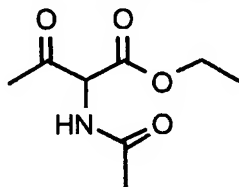
Phosphorus oxychloride (Aldrich Chemical Company)
(15 mL) 2,6-diphenylpyrrolo[3,2-d]pyrimidin-4-ol
5 (Example 45(b)) (0.40 g, 1.39 mmol) were added to a
round-bottomed flask. The resulting mixture was heated
at reflux under N₂ overnight. After cooling the
phosphorus oxychloride was removed under reduced
pressure to provide a brown oil. This material was
10 purified by flash chromatography on silica gel with
99:1 CHCl₃:MeOH as eluant to give 200 mg (48%) of the
title compound as a brown solid. Mp: 259-262 °C. ¹H NMR
(DMSO-d₆; 400 MHz): δ 7.28 (d, 1, J = 1.9), 7.47-7.58
(m, 6), 8.12 (d, 2, J = 7.3), 8.40 (2, dd, J = 1.6,
15 6.5), 12.53 (s, 1). MS m/z : 306 (M+1).



(d) 2,6-Diphenyl-4-piperidylpyrrolo[3,2-d]pyrimidine.

To a mixture of 4-chloro-2,6-diphenylpyrrolo[3,2-
d]pyrimidine (Example 45(c)) (123.9 mg, 0.41 mmol) and
20 piperidine (Aldrich Chemical Company) (200 µL, 2.03
mmol) was added a solution of K₂CO₃ (0.30 g, 2.18 mmol)
in H₂O (2.5 mL). This mixture was stirred at 140 °C in
a closed-capped Wheaton vial for 2.0 h. After cooling,
CH₂Cl₂ (10 mL) and H₂O (10 mL) were added. The organic
25 solution was removed and the aqueous solution washed

with CH_2Cl_2 (10 mL). The combined organic solutions were washed with saturated NaCl (15 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography silica gel 1:99 MeOH: CH_2Cl_2 as eluant to give 61 mg (42%) of the title compound as a white solid. Mp: 259-261.5 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.71 (br s, 6), 3.85 (br s, 4), 6.94 (d, 1, $J = 1.6$), 7.37-7.53 (m, 6), 7.94 (d, 2, $J = 8.3$), 8.40 (2, dd, $J = 1.4, 8.3$), 11.16 (s, 1). MS m/z : 355 (M+1). Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_4 \cdot 0.5\text{H}_2\text{O}$: C, 76.03; H, 6.34; N, 15.43. Found: C, 76.27; H, 6.34; N, 15.34.

Example 46

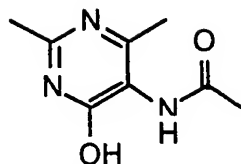
15

(a) Ethyl 2-(Acetylamino)-3-oxobutanoate.

This compound was prepared according to the method described in Example 1(b) by employing ethyl 2-hydroximino-3-oxobutanoate (25.2 g, 0.158 mol), H_2SO_4 (30% w/v) (230 g), crushed ice (240 g), and powdered zinc (100 mesh - Aldrich Chemical Company) (28.9 g). After filtration, the solution was treated with sodium acetate trihydrate (Aldrich Chemical Company) (148 g, 1.09 mol) and acetic anhydride (Aldrich Chemical Company) (18.2 g, 0.178 mol). The solution was stirred at room temperature for 0.25 h and worked-up as described in Example 1(b) to give 16.8 g (57%) of the title compound as a yellow oil after chromatography. ^1H NMR (CDCl_3 ; 500 MHz): δ 1.32 (t, 3, $J = 7.0$), 2.07 (s, 3), 2.40 (s, 3), 4.28 (q, 2, $J = 7.1$), 5.25 (d, 1, $J = 6.5$), 6.62 (br s, 1). MS m/z : 188 (M+1).

30

109



(b) 5-Acetamido-2,6-dimethyl-4-hydroxypyrimidine.

This compound was prepared according to the method described in Example 1(c) by mixing acetamidine hydrochloride (Aldrich Chemical Company) (5.1 g, 53.9 mmol) with a solution of sodium metal (2.2 g, 95.6 mmol) in absolute EtOH (95 mL). The suspension was filtered through celite and ethyl 2-(acetylamino)-3-oxobutanoate (8.4 g, 45.1 mmol) was added to the solution. After 18 hours, the reaction was concentrated to one half the original volume, H₂O (25 mL) was added, and the solution treated with HCl (conc.) to a pH of 4 (pH paper). Solids precipitated out of solution and were collected by vacuum filtration. The wet solids were recrystallized from EtOH and dried in a vacuum oven to give 5.2 g (64%) of the title compound as a white solid. The filtrate was concentrated with a rotary evaporator and recrystallized from EtOH to give an additional 1.2 g (14%) of the title compound as a white solid (total yield 6.4 g (78%)). Mp: 280-281 °C. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.98 (s, 3), 2.01 (s, 3), 2.24 (s, 3), 9.08 (s, 1), 12.46 (s, 1). MS m/z: 182 (M+1). Anal. Calcd for C₈H₁₁N₃O₂•0.75 H₂O: C 49.35, H 6.47, N 21.58. Found: C 49.62, H 6.21, N 21.68.

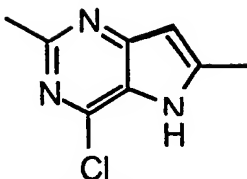


(c) 2,6-Dimethylpyrrolo[3,2-d]pyrimidin-4-ol.

This compound was prepared according to the method described in Example 1(d) by distilling to dryness a

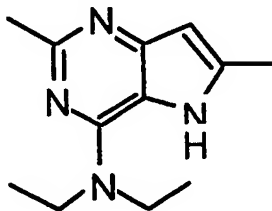
mixture of 5-acetamido-2,6-dimethyl-4-hydroxypyrimidine (4.8 g, 26.5 mmol) in a solution of sodium metal (1.82 g, 79.2 mmol) in absolute EtOH (40 mL). The white-yellow solids were scraped to the bottom of the flask and the residue heated at 360-400 °C for 20 min. H₂O (100 mL) was added to the hot residue and the pH was adjusted with HCl (conc.) to pH 4 (pH paper). The solvent was removed using the rotary evaporator and the resulting brown residue was dissolved in 1 N HCl (35 mL), treated with charcoal, and filtered through a plug of celite. The filtrate was adjusted to pH 8 with 10% NaOH and light brown crystals formed in the solution. The solids were collected by filtration and dried in a vacuum oven to give 0.85 g (20%) of the title compound as a light brown solid. The filtrate was concentrated to half of its original volume and a second crop of crystals was collected by filtration to give an additional 0.40 g (9%) of the title compound (total yield 1.2 g (29%)). ¹H NMR (DMSO-d₆; 500 MHz): δ 2.26 (s, 3), 2.29 (s, 3), 5.97 (s, 1), 11.57 (s, 1), 11.62 (s, 1). MS m/z: 164 (M+1). Anal. Calcd for C₈H₉N₃O: C, 58.89; H, 5.56; N 25.75. Found: C 58.62; H, 5.51; N, 25.56.

111



(d) 4-Chloro-2,6-dimethylpyrrolo[3,2-d]pyrimidine.

This compound was prepared according to the method described in Example 1(e) by employing 2,6-dimethylpyrrolo[3,2-d]pyrimidin-4-ol (1.1 g, 6.7 mmol), phosphorous oxychloride (Aldrich Chemical Company) (7.5 mL, 80.5 mmol), *N,N*-diethylaniline (Aldrich Chemical Company) (3.5 mL, 22.0 mmol), and 1,2-dichloroethane (10 mL) to give a brown oil. This crude material was purified by flash chromatography on silica gel with 5:1 hexanes:EtOAc followed by 1:1 hexanes:EtOAc to give 0.64 (52%) of the title compound as a clear glass. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 2.47 (s, 3), 2.57 (s, 3), 6.34 (s, 1), 12.04 (br s, 1). MS *m/z*: 182 (M+1).

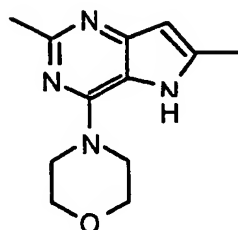


(e) (2,6-Dimethylpyrrolo[2,3-e]pyrimidin-4-yl)diethylamine.

To a 5-mL Wheaton vial was added 4-chloro-2,6-dimethylpyrrolo[3,2-d]pyrimidine (0.10 g, 0.55 mmol), diethylamine (Aldrich Chemical Company) (1.0 mL, 9.7 mmol), and absolute ethanol (1 mL). The reaction mixture was heated in the capped vial at reflux for 6 h. The reaction mixture was cooled to room temperature, diluted with H₂O (5 mL), and extracted twice with CH₂Cl₂. The organic layers were dried over MgSO₄, filtered, and concentrated with a rotary evaporator. The resulting orange-brown oil was recrystallized from EtOAc to give 0.050g (41%) of the title compound as a

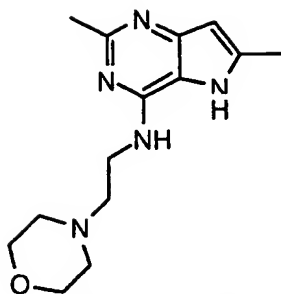
light brown solid. Mp: 212.5-213.5 °C. ¹H NMR (CDCl₃, 500 MHz): δ 1.31 (t, 6, J = 7.2), 2.43 (s, 3), 2.54 (s, 3), 3.70 (q, 4, J = 7.1), 6.19 (s, 1), 7.88 (br s, 1); MS m/z: 219 (M+1).

5

**Example 47****4-(2,6-Dimethylpyrrolo[2,3-e]pyrimidin-4-yl)morpholine.**

To a 5-mL Wheaton vial was added 4-chloro-2,6-dimethylpyrrolo[3,2-d]pyrimidine (Example 46(d)) (0.10 g, 0.55 mmol) and morpholine (Aldrich Chemical Company) (0.24 mL, 2.7 mmol). A solution of K₂CO₃ (0.35 g, 2.5 mmol) in water (2.5 mL) was added and the reaction mixture heated in the capped vial at reflux for 3.5 h. The reaction mixture was cooled to room temperature and the solution was filtered. The resulting precipitate was washed with H₂O and hexanes and dried in a 60 °C vacuum oven to give 0.083 g (65%) of the title compound as an off-white solid. Mp: 242-243 °C. ¹H NMR (DMSO-d₆; 500 MHz): δ 2.39 (s, 6), 3.60 (s, 4), 3.74 (s, 4), 6.07 (s, 1), 10.90 (s, 1). MS m/z: 233 (M+1). Anal. Calcd for C₁₂H₁₆N₄O: C, 59.73; H, 7.10; N, 23.22. Found: C, 60.01; H, 6.84; N, 23.29.

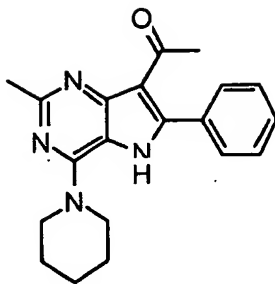
113

**Example 48**

(2,6-Dimethylpyrrolo[2,3-e]pyrimidin-4-yl)(2-morpholin-4-ylethyl)amine.

- 5 This compound was prepared according to the method described in Example 46(e) by employing 4-chloro-2,6-dimethylpyrrolo[3,2-d]pyrimidine (Example 46(d)) (0.10 g, 0.55 mmol) with 4-(2-aminoethyl)morpholine (Aldrich Chemical Company) (0.388 mL, 2.95 mmol) and K_2CO_3 (0.36 g, 2.6 mmol) in water (2.5 mL) to give 0.038g (25%) of the title compound as an off-white solid after recrystallization from EtOAc. Mp: 237-238.5 °C. 1H NMR (CDCl₃; 500 MHz): δ 2.43 (s, 3), 2.50 (t, 4, J = 5.2), 2.58 (s, 3), 2.65 (t, 2, J = 5.7), 3.67 (t, 4, J = 4.6), 3.70 (q, 2, J = 5.4), 5.55 (br s, 1), 6.18 (s, 1), 9.88 (br s, 1). MS m/z : 276 (M+1). Anal. Calcd for C₁₄H₂₁N₅O: C, 61.07; H, 7.69; N 25.43. Found: C, 61.19; H, 7.77; N, 25.39.
- 10
- 15

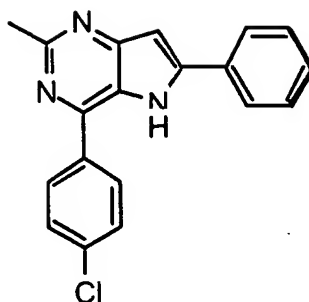
114

**Example 49****7-Acetyl-2-methyl-6-phenyl-4-piperidylpyrrolo
[3,2-d]pyrimidine.**

5 A mixture of 2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 35) (50 mg, 0.17 mmol), acetic anhydride (Aldrich Chemical Company) (168 mg, 1.64 mmol, 9.7 eq), K_2CO_3 (227 mg, 1.64 mmol, 9.7 eq) and 4-*N,N*-dimethylaminopyridine (2.6 mg, 0.021 mmol, 0.12 eq) in anhydrous DMF (2.0 mL) was stirred under N_2 at 110 °C overnight. After cooling to the room temperature, the reaction was quenched by the addition of saturated $NaHCO_3$ (5 mL) and extracted with $CHCl_3$ (3 x 30 mL). The organic layers were washed with saturated NaCl, dried over Na_2SO_4 and concentrated with a rotary evaporator. The crude material was purified by flash chromatography on silica gel with a gradient eluant of EtOAc(0-25%):hexanes(100-75%) to afford 13 mg (22%) of the title compound as an off-white solid. Mp: 188-190 °C. 1H NMR ($CDCl_3$; 400 MHz): δ 11.43 (s, 1), 7.61 (d, 2, $J = 7.4$), 7.43 (t, 2, $J = 7.4$), 7.37 (t, 1, $J = 7.4$), 4.88 (br s, 2), 4.06 (br s, 2), 2.58 (s, 3), 2.11 (s, 3), 1.73 (br s, 6). MS m/z : 335 ($M+1$), 333 ($M-1$). HRMS (NBA-NaI) m/z Calcd for $M+H$, $C_{20}H_{22}N_4O$: 335.1888.

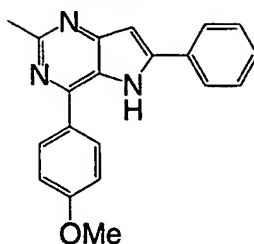
25 Found: 335.1872.

115

**Example 50****4-(4-Chlorophenyl)-2-methyl-6-phenylpyrrolo
[3,2-d]pyrimidine.**

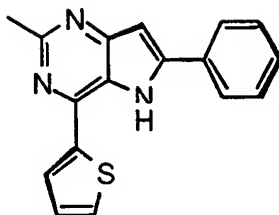
5 A mixture of 4-chloro-2-methyl-6-phenylpyrrolo
[3,2-d]pyrimidine (Example 1(e)) (50 mg, 0.21 mmol), 4-
chlorophenylboronic acid (Aldrich Chemical Company) (39
mg, 0.25 mmol), tris(dibenzylidene-neacetone)
dipalladium(0) (Aldrich Chemical Company) (4.7 mg,
10 0.0051 mmol) and triphenylphosphine (Aldrich Chemical
Company) (5.4 mg, 0.021 mmol) in a mixed solvent (600
 μ L of toluene, 300 μ L of 1.0 M Na_2CO_3 , and 150 μ L of
ethanol) was heated at reflux under N_2 for 20 h. Upon
cooling to the room temperature, the reaction mixture
15 was diluted with H_2O (20 mL) and extracted with CHCl_3 (3
x 15 mL), dried over Na_2SO_4 and concentrated with a
rotary evaporator. The crude material was purified by
flash chromatography on silica gel with a gradient
eluant of EtOAc(0-25%):hexanes(100-75%) to afford 32 mg
20 (49%) of the title compound as a yellow solid. Mp:
281-283 $^\circ\text{C}$. ^1H NMR (Acetone- d_6 ; 400 MHz): δ 10.89 (s,
1), 8.18 (d, 2, J = 8.5), 8.02 (d, 2, J = 7.4), 7.60
(d, 2, J = 8.5), 7.53 (t, 2, J = 7.4) 7.46 (t, 1, J =
7.4), 7.01 (s, 1), 2.72 (s, 3). MS m/z : 320 (M+1), 318
25 (M-1). HRMS (NBA-NaI) m/z Calcd for $\text{M}+\text{H}$, $\text{C}_{19}\text{H}_{14}\text{ClN}_3$:
320.0955. Found: 320.0961.

Example 51

**4-(4-Methoxyphenyl)-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine.**

- 5 A mixture of 4-chloro-2-methyl-6-phenylpyrrolo-
[3,2-d]pyrimidine (Example 1(e)) (50 mg, 0.21 mmol),
4-methoxyphenylboronic acid (Aldrich Chemical Company)
(44 mg, 0.287 mmol), tris(dibenzylideneacetone)
dipalladium(0) (Aldrich Chemical Company) 4.7 mg,
10 0.0051 mmol, 0.025 eq) and triphenylphosphine (Aldrich
Chemical Company) (10.8 mg, 0.041 mmol) in a mixed
solvent (600 μ L of toluene, 300 μ L of 1.0 M Na_2CO_3 , and
150 μ L of ethanol) was heated at reflux under N_2 for 36
h. Upon cooling to the room temperature, the reaction
15 mixture was diluted with H_2O (20 mL) and extracted with
 CHCl_3 (3 x 20 mL). The organic phase was dried over
 Na_2SO_4 , filtered, and concentrated with a rotary
evaporator. The crude material was purified by flash
chromatography on silica gel with a gradient eluant of
20 EtOAc (0-50%):hexanes(100-50%) to afford 57 mg (89%) of
the title compound as a yellow solid. Mp: 225-227 $^\circ\text{C}$.
 ^1H NMR (Acetone- d_6 , 400 MHz): δ 10.72 (s, 1), 8.14 (d,
2, J = 7.0), 8.00 (d, 2, J = 8.0), 7.51 (t, 2, J =
7.0), 7.44 (t, 1, J = 7.0), 7.11 (d, 2, J = 8.0), 6.95
25 (s, 1), 3.91 (s, 3), 2.70 (s, 3). MS m/z : 320 ($\text{M}+1$),
318 ($\text{M}-1$). HRMS (NBA- NaI) m/z Calcd for $\text{M}^+ + \text{H}$,
 $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}$: 316.1450. Found: 316.1450.

117

**Example 52****2-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)thiophene.**

5 A mixture of 4-chloro-2-methyl-6-phenylpyrrolo-[3,2-d]pyrimidine (Example 1(e)) (50 mg, 0.21 mmol), thiophene-2-boronic acid (37 mg, 0.287 mmol), tris(dibenzylidene-acetone)dipalladium(0) (Aldrich Chemical Company) (4.7 mg, 0.0051 mmol) and

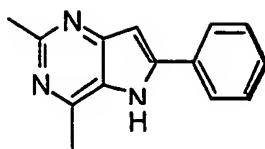
10 triphenylphosphine (Aldrich Chemical Company) (10.8 mg, 0.041 mmol) in a mixed solvent (600 μ L of toluene, 300 μ L, 1.0 M Na_2CO_3 and 150 μ L of ethanol) was heated at reflux under N_2 for 36 h. Upon cooling to the room temperature, the reaction mixture was diluted with H_2O

15 (20 mL) and extracted with CHCl_3 (3 x 20 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated with a rotary evaporator. The crude material was purified by flash chromatography on silica gel with a gradient eluant of EtOAc(0-25%):hexanes(100-

20 75%) to afford 37.2 mg (62%) of the title compound as a yellow solid. Mp: 178-179 $^\circ\text{C}$. ^1H NMR (Acetone- d_6 ; 400 MHz): δ 10.61 (s, 1), 8.21 (d, 1, J = 4.5), 8.00 (d, 2, J = 7.3), 7.73 (d, 2, J = 4.5), 7.54 (t, 2, J = 7.3), 7.48 (t, 1, J = 7.3) 7.28 (t, 1, J = 4.5), 6.96 (s, 1),

25 2.68 (s, 3). MS m/z : 292 (M+1), 290 (M-1). HRMS (NBA-NaI) m/z Calcd for $\text{M}+\text{H}$, $\text{C}_{17}\text{H}_{13}\text{N}_3\text{S}$: 292.0908. Found: 292.0900.

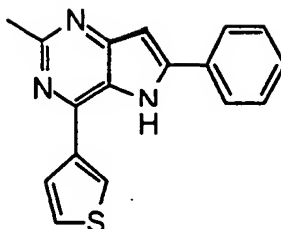
118

**Example 53****2,4-Dimethyl-6-phenylpyrrolo[3,2-d]pyrimidine.**

A mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (80 mg, 0.33 mmol), methylboronic acid (Aldrich Chemical Company) (49 mg, 0.82 mmol), tris(dibenzylideneacetone)dipalladium(0) (Aldrich Chemical Company) (9.4 mg, 0.0103 mmol) and triphenylphosphine (Aldrich Chemical Company) (10.8 mg, 0.042 mmol) in a mixed solvent (1000 μ L of toluene, 500 μ L of 1.0 M Na_2CO_3 , and 250 μ L of ethanol) was heated at reflux under N_2 overnight. Upon cooling to the room temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with CHCl_3 (4 x 40 mL). The organic extracts were dried over Na_2SO_4 , filtered, and concentrated with a rotary evaporator. This material was purified by preparative thin layer chromatography on silica gel with 1:1 THF:hexanes as eluant to afford 30 mg (62%) of the title compound as a yellow solid. ^1H NMR (CDCl_3 ; 400 MHz): δ 8.38 (s, 1), 7.74 (d, 2, $J = 7.0$), 7.53 (t, 2, $J = 7.0$), 7.45 (t, 1, $J = 7.0$), 6.87 (d, 1, $J = 1.7$), 2.79 (s, 3), 2.74 (s, 3). MS m/z : 224 ($M+1$), 222 ($M-1$).

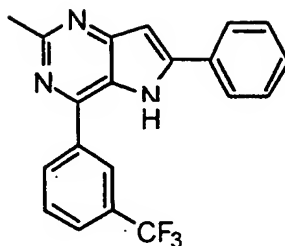
25

119

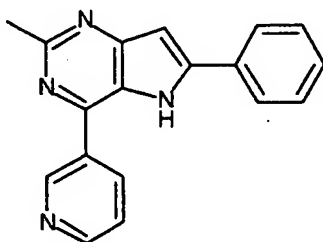
**Example 54****3-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)thiophene.**

- 5 A mixture of 4-chloro-2-methyl-6-phenyl-pyrrolo[3,2-d]pyrimidine (Example 1(e)) (50 mg, 0.21 mmol), thiophene-3-boronic acid (37 mg, 0.287 mmol), tris(dibenzylidene-acetone)dipalladium(0) (Aldrich Chemical Company) (4.7 mg, 0.0051 mmol, 0.025 eq) and
- 10 triphenylphosphine (Aldrich Chemical Company) (10.8 mg, 0.041 mmol, 0.2 eq) in a mixed solvent (600 μ L of toluene, 300 μ L of 1.0 M Na_2CO_3 , and 150 μ L of ethanol) was heated at reflux under N_2 for 17 h. Upon cooling to the room temperature, the reaction mixture was
- 15 diluted with H_2O (20 mL) and extracted with CHCl_3 (3 x 20 mL). The organic phase was dried over Na_2SO_4 , filtered and concentrated with a rotary evaporator. The crude material was purified by flash chromatography on silica gel a gradient eluant of EtOAc(0-
- 20 25%):hexanes(100-75%) to afford 43.3 mg (73%) of an off-white solid. Mp: 232-233 $^\circ\text{C}$. ^1H NMR (CDCl_3 ; 400 MHz): δ 8.57 (s, 1), 8.04 (dd, 1, J = 1.2, 2.9), 7.66 (m, 3), 7.59 (dd, 1, J = 2.9, 5.0), 7.52 (t, 2, J = 7.7), 7.46 (t, 1, J = 7.7), 6.94 (d, 1, J = 2.0), 2.86
- 25 (s, 3). MS m/z : 292 (M+1), 290 (M-1).

120

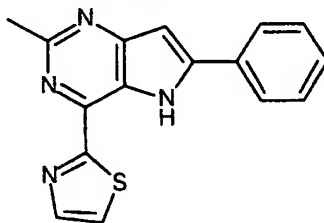
**Example 55****2-Methyl-6-phenyl-4-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidine.**

- 5 A mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (50 mg, 0.21 mmol), 3-(trifluoromethyl)phenylboronic acid (Fluka) (55 mg, 0.287 mmol, 1.4 eq), tris(dibenzylideneacetone)dipalladium (0) (Aldrich
- 10 Chemical Company) (4.7 mg, 0.0051 mmol, 0.025 eq) and triphenylphosphine (Aldrich Chemical Company) (10.8 mg, 0.041 mmol, 0.2 eq) in a mixed solvent (600 μ L of toluene, 300 μ L of 1.0 M Na_2CO_3 , and 150 μ L of ethanol) was heated at reflux under N_2 for 19 h. Upon cooling
- 15 to the room temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with CHCl_3 (3 x 20 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated with a rotary evaporator.
- Mp: 206-208 $^\circ\text{C}$. ^1H NMR (CDCl_3 , 400 MHz): δ 8.58 (s, 1), 8.28 (s, 1), 8.18 (d, 1, J = 7.6), 7.82 (d, 1, J = 7.8), 7.77-7.72 (m, 3), 7.53 (t, 2, J = 7.4), 7.46 (t, 1, J = 7.4), 6.98 (d, 1, J = 2.0), 2.89 (s, 3). MS m/z : 354 (M+1), 352 (M-1).
- 20



Example 56**2-Methyl-6-phenyl-4-(3-pyridinyl)pyrrolo[3,2-d]pyrimidine.**

A mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (230 mg, 0.94 mmol), 3-pyridinylboronic acid (Frontier Scientific) (139 mg, 1.13 mmol), tris(dibenzylideneacetone)dipalladium(0) (Aldrich Chemical Company) (22 mg, 0.024 mmol) and triphenylphosphine (Aldrich Chemical Company) (49 mg, 0.19 mmol) in a mixture of solvents (1.2 mL of toluene, 0.3 mL of 1.0 M Na₂CO₃ and 0.3 mL of ethanol) was heated at reflux under N₂ for 40 h. Upon cooling to the room temperature, the reaction mixture was diluted with H₂O (20 mL), and the crude product was extracted with CHCl₃ (3 x 40 mL). The organic extracts were washed with H₂O (50 mL), saturated NaCl (50 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator. Chromatography on silica gel with a gradient eluant of MeOH (0-4%):CH₂Cl₂ (100-96%) afforded 171 mg (64%) of the title compound as a yellow solid. Mp: 252-254 °C. ¹H NMR (CDCl₃; 400 MHz): δ 2.89 (s, 3), 6.99 (s, 1), 7.46 (m, 4), 7.78 (d, 2, J = 7.1), 8.37 (d, 1, J = 7.7), 8.66 (d, 1, J = 3.9), 9.31 (s, 1), 9.50 (s, 1). MS m/z: 287 (M+1), 285 (M-1). HRMS: Calcd for M+H: 287.1297. Found: 287.1288.

Example 57

2-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-1,3-thiazole.

A mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (200 mg, 0.82 mmol), 2-tributylstannylthiazole (Frontier Scientific) (338 mg, 0.90 mmol),

5 tris(dibenzylideneacetone)dipalladium(0) (Aldrich Chemical Company) (19 mg, 0.021 mmol) and triphenylphosphine (Aldrich Chemical Company) (43 mg, 0.16 mmol) in anhydrous toluene (2 mL) was refluxed under N₂ for 4 d. TLC showed that the reaction was not

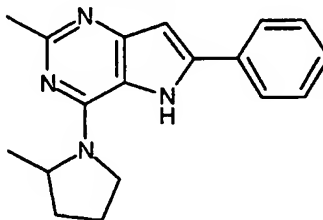
10 complete. Therefore, additional portions of 2-tributylstannylthiazole (338 mg, 0.90 mmol), tris(dibenzylideneacetone)dipalladium(0) (19 mg, 0.021 mmol) and triphenylphosphine (43 mg, 0.16 mmol) were added to the reaction mixture, and the mixture was

15 stirred at 120 °C for 3 d. Upon cooling to the room temperature, the reaction was quenched with 5% HCl (50 mL) and the solution was extracted with CHCl₃ (3 x 100 mL). The organic extracts were washed with H₂O (2 x 150 mL), filtered through a pad of Celite, washed with

20 saturated NaCl (150 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator. Chromatography on silica gel with a gradient eluant of MeOH (1-3%):CH₂Cl₂ (99-97%) afforded 119 mg (50%) of the title compound as a yellow solid. Mp: 248-250 °C. ¹H NMR

25 (acetone-d₆; 400 MHz): δ 2.69 (s, 3), 7.01(s, 1), 7.57-7.47 (m, 3), 8.06 (d, 2, J = 7.17), 8.97 (s, 1), 9.18 (s, 1), 10.76 (s, 1). MS m/z: 293 (M+1), 291 (M-1). HRMS: Calcd for M+H: 293.0861. Found: 293.0866.

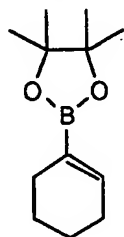
30

Example 58

2-Methyl-4-(2-methylpyrrolidin-1-yl)-6-phenylpyrrolo[3,2-d]pyrimidine.

A mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (230 mg, 0.94 mmol), 2-methylpyrrolidine (Alfa) (799 mg, 9.4 mmol), K_2CO_3 (650 mg, 4.7 mmol) in H_2O (1.5 mL) was stirred at 105 °C for 20 h. Upon cooling to room temperature, the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 x 15 mL). The organic phase was washed with H_2O (20 mL), saturated NaCl (20 mL), dried over Na_2SO_4 , and concentrated with a rotary evaporator. Chromatography on silica gel with a gradient eluant of MeOH (0-10%): CH_2Cl_2 (100-90%) afforded 250 mg (93%) of the title compound as an off-white solid. Mp: 219-221 °C. 1H NMR ($CDCl_3$; 400 MHz): δ 1.39 (d, 3, J = 6.3), 1.79 (m, 1), 2.22-2.07 (m, 3), 2.58 (s, 3), 3.90 (m, 1), 4.04 (m, 1), 4.59 (m, 1), 6.74 (s, 1), 7.38 (t, 1, J = 7.4), 7.46 (t, 2, J = 7.4), 7.63 (d, 2, J = 7.4), 8.31 (s, 1). MS m/z : 293 (M+1), 291 (M-1). HRMS: Calcd for M+H: 293.1766. Found: 293.1770.

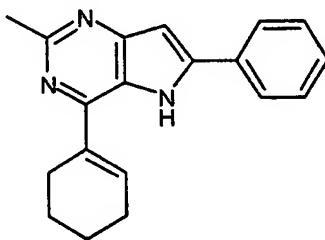
Example 59



(a) 2-Cyclohex-1-enyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

A mixture of cyclohexenyl trifluoroacetate (1360 mg, 5.91 mmol, 1.0 eq), bis(pinacolacto)diboron (Ryan scientific) (1652 mg, 6.5 mmol, 1.1 eq), dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II)

dichloromethane adduct [PdCl₂(dppf)] (Aldrich Chemical Company) (145 mg, 0.177 mmol, 0.03 eq), potassium acetate (Aldrich Chemical Company) (1740 mg, 17.73 mmol, 3.0 eq) in anhydrous dimethyl sulfoxide (10 mL) was stirred under nitrogen at 70 °C for overnight. Upon cooling to the room temperature, the reaction mixture was diluted with H₂O (30 mL), and the crude product was extracted with benzene (3 x 40 mL). The organic extracts were washed with H₂O (3 x 40 mL), saturated NaCl (50 ml), and dried over Na₂SO₄ and concentrated in vacuo. Bulb-to-bulb distillation (oven temperature 90-100°C) afforded 1065 mg (85%) of the title compound as a colorless oil. ¹H NMR (CDCl₃; 400 MHz): δ 6.56 (s, 1), 2.09 (bs, 4), 1.59 (m, 4), 1.26 (s, 12).

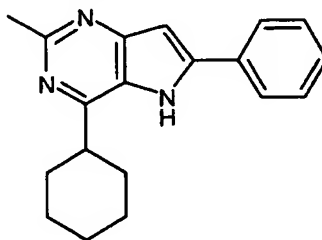


(b) 4-Cyclohex-1-enyl-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine.

A mixture of 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (261 mg, 1.03 mmol), 2-cyclohex-1-enyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Example 59 (a)) (237 mg, 1.13 mmol, 1.04 eq), tris(dibenzylideneacetone)dipalladium(0) (Aldrich Chemical Company) (25 mg, 0.027 mmol) and triphenylphosphine (Aldrich Chemical Company) (56 mg, 0.21 mmol) in a mixture of solvents (1.2 mL of toluene, 0.3 mL of 1.0 M Na₂CO₃ and 0.3 mL of ethanol) was refluxed under N₂ for 2 d. Upon cooling to room temperature, the reaction mixture was diluted with H₂O

(40 mL) and the solution was extracted with CHCl₃ (4 x 40 mL). The organic extracts were washed with water (50 mL), saturated NaCl (50 mL), dried over Na₂SO₄ and concentrated with a rotary evaporator. Chromatography on silica gel with a gradient eluant of EtOAc (0-30%):hexanes (100-70%) afforded 153 mg (48%) of the title compound as an off-white solid. Mp: 247-249 °C. ¹H NMR (CDCl₃; 400 MHz): δ 1.79 (m, 2), 1.88 (m, 2), 2.36 (m, 2), 2.68 (m, 2), 2.79 (s, 3), 6.63 (m, 1), 6.87 (d, 1, J = 2.0), 7.45 (t, 2, J = 7.2), 7.49 (t, 2, J = 7.2), 7.72 (d, 2, J = 7.2), 8.47 (s, 1). MS m/z: 290 (M+1), 288 (M-1). HRMS: Calcd for M+H: 290.1657. Found: 290.1657.

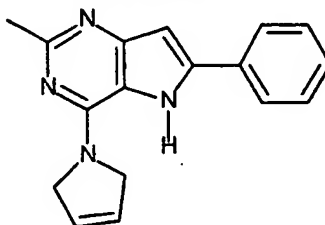
15

Example 60**4-Cyclohexyl-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine.**

A solution of 2-methyl-4-(1-cyclohexenyl)-5H-6-phenylpyrrolo[3,2-d]pyrimidine (Example 59) (96 mg, 0.33 mmol) in ethanol (5 mL) was agitated on a Parr Apparatus at room temperature in the presence of PtO₂ (Aldrich Chemical Company) (20 mg, 0.088 mmol) under H₂ (70 psi) for 30 h. The reaction mixture was filtered through a pad of Celite and concentrated on a rotary evaporator. Chromatography on silica gel with a gradient eluant of EtOAc (0-20%):hexanes (100-80%) afforded 55 mg (57%) of the title compound as an off-white solid. Mp: >280 °C. ¹H NMR (CDCl₃; 400 MHz): δ 1.44-1.49 (m, 2), 1.81-1.88 (m, 4), 1.93-2.01 (m, 4),

2.99 (m, 1), 6.86 (d, 1, $J = 1.4$), 7.44 (t, 1, $J = 6.1$), 7.51 (t, 2, $J = 6.1$), 7.74 (d, 2, $J = 6.1$), 8.40 (s, 1). MS m/z : 292 (M+1), 290 (M-1). HRMS: Calcd for M+H: 292.1814. Found: 292.1806.

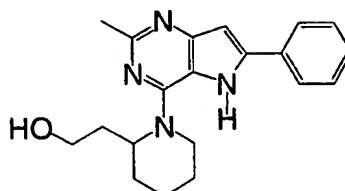
5

Example 61**2-Methyl-6-phenyl-4-(pyrrolinyl)pyrrolo(3,2-d)pyrimidine Hydrochloride Monohydrate.**

10 To a oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (250 mg, 1.03 mmol) and pyrroline (Aldrich Chemical Company) (1.00 mL, 13.1 mmol). The flask was purged with N_2 and the solution
15 was heated at 180 °C for 2 h. The reaction was cooled to room temperature and the crude material was purified by flash chromatography on silica gel with 1:1 EtOAc:hexanes as eluant to give 283 mg (100%) of a light yellow solid. The product (282 mg, 1.03 mmol)
20 was dissolved in MeOH (8 mL) and anhydrous ethereal HCl (Aldrich Chemical Company) (1.05 mL of a 1 M soln, 1.05 mmol) was added dropwise. The mixture was stirred for 18 h at room temperature. The solvent was evaporated in vacuo, and the solid was recrystallized
25 from EtOAc/MeOH to give 240 mg (85%) of the title compound as an off-white solid. Mp: 278-278.3 °C. 1H NMR (DMSO- d_6 ; 400 MHz): δ 2.60 (s, 3), 4.59 (br s, 2), 5.05 (br s, 2), 6.12 (s, 2), 6.91 (s, 1), 7.49-7.58 (m, 3), 7.97 (d, 2, $J = 7.2$), 11.62 (s, 1). MS m/z :
30 277(M+1), 275 (M-1). Anal. Calcd for

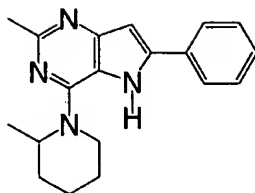
$C_{17}H_{16}N_4 \cdot 1.1HCl \cdot H_2O$: C, 61.05; H, 5.76; N, 16.76; Cl, 11.66. Found: C, 60.92; H, 5.39; N, 16.36; Cl, 11.53.

5

Example 62**2-Methyl-6-phenyl-4-(2-piperidineethanol)pyrrolo
(3,2-d)pyrimidine Hydrochloride.**

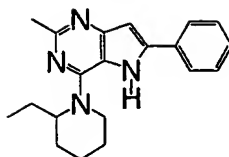
To a oven-dried, 50-mL, round-bottomed flask was
10 added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-
d]pyrimidine (Example 1(e)) (250 mg, 1.03 mmol) and 2-
piperidine ethanol (Aldrich Chemical Company) (435 mg,
3.06 mmol). The flask was purged with N_2 , and the
solution was heated at 190 °C for 2 h. The reaction
15 was cooled to room temperature and the crude material
was purified by flash chromatography on silica gel
with 1:1 EtOAc:hexanes as eluant to give 115 mg (33%)
of a light-yellow solid. The product (43 mg, 0.128
mmol) was dissolved in CH_2Cl_2 (5 mL) and anhydrous
20 etheral HCl (Aldrich Chemical Company) (0.128 mL of a
1M soln, 0.128 mmol) was added dropwise. The mixture
was stirred for 18 h at room temperature. The solvent
was evaporated and the solid was recrystallized from
EtOAc/MeOH to give 39 mg (11%) of product. Mp: 273-
25 273.5 °C. 1H NMR ($DMSO-d_6$; 400 MHz): δ 1.34-2.12 (m,
6H); 2.38 (s, 3), 2.47-3.55 (m, 5), 4.67 (br d, 2),
6.76 (s, 1), 7.29-7.36, (m, 3), 7.72 (d, 2, $J = 6.72$),
12.35 (br s, 1), 14.02 (br s, 1). MS m/z : 337(M+1),
335 (M-1). Anal. Calcd for $C_{20}H_{23}N_4 \cdot HCl$: C, 64.42; H,
30 6.76; N, 15.03. Found: C, 63.98; H, 6.76; N, 14.65.

128

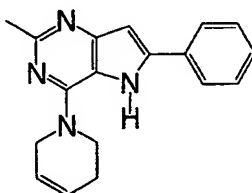
**Example 63****2-Methyl-6-phenyl-4-(2-methylpiperidinyl)pyrrolo(3,2-d)pyrimidine Hydrochloride Monohydrate.**

- 5 To a oven dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (250 mg, 1.03 mmol) and 2-methylpiperidine (Aldrich Chemical Company) (250 mg, 2.46 mmol). The flask was purged with N₂, and the
- 10 solution was heated at 190 °C for 2 h. The reaction was cooled to room temperature and the crude material was purified by flash chromatography on silica gel with EtOAc as the eluant to give 214 mg (84% yield) of the free base as a white solid. The product (205 mg,
- 15 0.67 mmol) was dissolved in EtOAc (5 mL) and anhydrous ethereal HCl (Aldrich Chemical Company) (0.67 mL of a 1 M soln, 0.67 mmol) was added dropwise. The mixture was stirred for 18 h at room temperature. The solvent was evaporated *in vacuo* and the solid was
- 20 recrystallized from EtOAc/MeOH to give 200 mg (71%) of product. Mp: 268-269 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.17 (d, 3, J = 6.8), 1.31-1.82 (m, 8), 2.41 (s, 3), 3.3 (br s, 1), 4.46 (br s, 1), 5.11 (br s, 1), 6.72 (s, 1), 7.34-7.42 (m, 3), 7.77 (d, 2, J = 7.27),
- 25 11.71. MS m/z : 307 (M+1). Anal. Calcd for C₁₉H₂₂N₄•HCl•H₂O: C, 63.23; H, 6.98; N, 15.53; Cl, 9.82. Found: C, 62.82; H, 6.39; N, 15.38; Cl, 9.93.

129

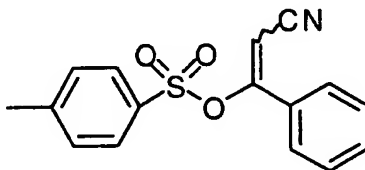
**Example 64****2-Methyl-6-phenyl-4-(2-ethylpiperidinyl)pyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

- 5 To a oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (250 mg, 1.03 mmol) which was dissolved in 2-ethylpiperidine (Aldrich Chemical Company) (1.00 mL, 7.5 mmol). The flask was purged with nitrogen and
- 10 the solution was heated at 190 °C for 2 h. The reaction was cooled to room temperature and chromatographed using EtOAc as the eluant afforded 307 mg (94%) of a light-yellow solid. The product (300 mg, 0.94 mmol) was dissolved in CH₂Cl₂ (7 mL) and
- 15 anhydrous ethereal HCl (Aldrich) (0.94 mL of a 1 M soln, 0.94 mmol) was added dropwise. The mixture was stirred for 18 h at room temperature. The solvent was evaporated *in vacuo* and the solid was recrystallized from EtOAc/MeOH to give 280 mg (74%) of product. Mp:
- 20 228-229 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 0.83 (t, 3, *J* = 7.23); 1.63-1.95 (m, 8), 2.57 (s, 3), 3.37 (br s, 3), 4.56-5.13 (br d, 2), 6.89 (s, 1), 7.5-7.58 (m, 3), 7.94 (d, 2, *J* = 7.3), 11.96 (br s, 1). MS *m/z* : 321 (M+1). Anal. Calcd for C₂₀H₂₄N₄•HCl•0.5H₂O: C, 65.6; H, 7.08; N, 15.14; Cl, 9.81. Found: C, 65.81; H, 6.86; N, 15.20; Cl, 9.61.
- 25



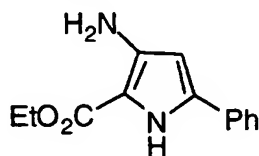
Example 65**2-Methyl-6-phenyl-4-(1,2,3,6-tetrahydropyridinyl) pyrrolo[3,2-d]pyrimidine Hydrochloride.**

To a oven-dried, 50-mL, round-bottomed flask was added
5 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine
(Example 1(e)) (250 mg, 1.03 mmol) which was dissolved
in 1,2,3,6-tetrahydropyridine (Aldrich Chemical
Company) (580 mg, 7.00 mmol). The flask was purged
with N₂ and heated at 190 °C for 2 h. After cooling to
10 room temperature, the reaction mixture was
chromatographed with 1:1 EtOAc:hexanes as the eluant
to afford 310 mg (87%) of a light-yellow solid. The
product (300 mg, 1.03 mmol) was dissolved in
EtOAc:CHCl₃ (5:15 mL) and anhydrous ethereal HCl (1.1
15 mL of a 1 M soln, 1.1 mmol) was added dropwise. The
mixture was stirred for 18 h at room temperature. The
sample was concentrated in vacuo and the solid was
recrystallized from EtOAc/MeOH to give 287 mg (74%) of
product. Mp: 278-279 °C. ¹H NMR (DMSO-d₆; 400 MHz):
20 δ 2.57 (s, 2), 2.8 (s, 3), 4.38 (t, 2, J = 5.53), 4.86
(s, 2), 6.1 (d, 1, J = 10.2), 6.2 (d, 2, J = 10), 7.14
(s, 1), 7.72-7.81 (m, 3), 8.2 (d, 2, J = 7.2), 12.18
(s, 1), 14.81 (br s, 1). MS m/z: 291(M+1), 289 (M-1).
Anal. Calcd for C₁₈H₁₈N₄•HCl: C, 63.35; H, 6.09; N,
25 16.42. Found: C, 63.05; H, 5.64; N, 16.24.

Example 66**(a) 2-Cyano-1-phenylvinyl 4-methylbenzenesulfonate.**

30 To a 100-mL, round-bottomed flask were added
benzoyl acetonitrile (Aldrich Chemical Company) (3.4

g, 23 mmol), *p*-toluenesulfonyl chloride (Aldrich Chemical Company) (5.1 g, 27 mmol) and CH_2Cl_2 (50 mL). After colling the flask in an ice bath, Et_3N (3.3 mL, 23 mmol) was added dropwise to the solution. The
5 mixture was stirred for 1 h, and stirred at room temperature for 22 h. Water and CH_2Cl_2 were added, and the organic layer was separated, washed three times with water, dried over Na_2SO_4 and concentrated *in vacuo* to give an orange solid. Flash chromatography on
10 silica gel using 10:1 hexane:EtOAc as eluant afforded 4.0 g (57%) of the title compound as a yellow solid.
 ^1H NMR (CDCl_3 ; 400 MHz): δ 2.46 (d, 3), 5.57 (d, 1), 7.31-7.50 (m, 5), 7.58 (d, 1, $J = 7.93$), 7.65 (d, 1, $J = 7.92$), 7.76 (d, 1, $J = 8.22$), 7.90 (d, 1, $J = 8.26$).
15 MS m/z : 300 ($M+1$), 298 ($M-1$).



(b) Ethyl 3-amino-5-phenylpyrrole-2-carboxylate.

Sodium ethoxide was prepared freshly from Na (0.92 g, 40 mmol) and EtOH (25 mL). To the above
20 solution was added a solution of 2-cyano-1-phenylvinyl 4-methylbenzenesulfonate (Example 66 (a)) (4.0 g, 13 mmol), aminodiethyl malonate hydrochloride (Aldrich Chemical Company) (2.8 g, 13 mmol) in EtOH (70 mL) and THF (6 mL) through a dropping funnel. After the
25 addition was completed, the reaction mixture was stirred at room temperature for 2 h. A precipitate was then removed from the reaction mixture by filtration, and the filtrate was concentrated *in vacuo* to give an orange solid. Water was added and the
30 mixture was extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give 3.0 g of crude product as an orange

solid. This material was used directly in the following step without purification. An analytical sample was obtained as off-white crystals by recrystallization from toluene:cyclohexane. ¹H NMR

- 5 (DMSO-d₆; 400 MHz): δ 1.28 (t, 3, J = 7.12), 4.22 (q, 2, J = 7.20), 5.06 (br s, 2), 5.98-6.03 (m, 1), 7.16-7.38 (m, 3), 7.72-7.76 (m, 2), 10.68 (br s, 1); MS m/z: 231 (M+1), 229 (M-1).

- 10 The following compounds were also prepared using the method described in Example 66(b):

Ethyl 3-amino-5-(3-methylphenyl)pyrrole-2-carboxylate: MS (ESI) m/z: 244 (M⁺); Anal. Calcd for C₁₄H₁₆N₂O₂: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.74; H, 6.72; N, 11.29;

- 15 Ethyl 3-amino-5-(2-chlorophenyl)pyrrole-2-carboxylate: MS (ESI) m/z: 265 (M+1); Anal. Calcd for C₁₃H₁₃ClN₂O₂: C, 58.99; H, 4.95; N, 10.58; Cl, 13.39. Found: C, 58.80; H, 5.08; N, 10.40; Cl, 13.17;

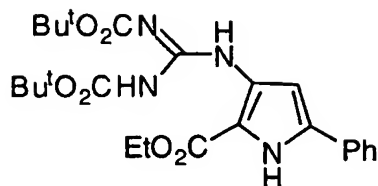
- 20 Ethyl 3-amino-5-(2-furyl)pyrrole-2-carboxylate: MS (ESI) m/z: 221 (M+1); Anal. Calcd for C₁₁H₁₂N₂O₃: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.95; H, 5.55; N, 12.79;

- 25 Ethyl 3-amino-5-(2-thienyl)pyrrole-2-carboxylate: MS (ESI) m/z: 237 (M+1); Anal. Calcd for C₁₁H₁₂N₂O₂S: C, 55.92; H, 5.12; N, 11.86; S, 13.57. Found: C, 56.04; H, 5.04; N, 11.75; S, 13.60;

Ethyl 3-amino-5-(tert-butyl)pyrrole-2-carboxylate: MS (HRMS) m/z: 211.1446 (expected), 211.1443 (observed); and

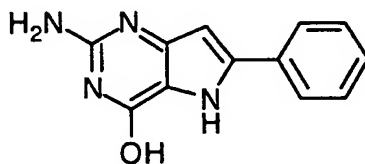
- 30 Ethyl 3-amino-4-methyl-5-phenylpyrrole-2-carboxylate: MS (ESI) m/z: 244 (M⁺); Anal. Calcd for C₁₄H₁₆N₂O₂: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.06; H, 6.47; N, 11.54.).

133



(c) **tert-Butyl 2-aza-3-[(tert-butoxy)carbonylamino]-3-{[2-(ethoxycarbonyl)-5-phenylpyrrol-3-yl]amino}prop-2-enoate.**

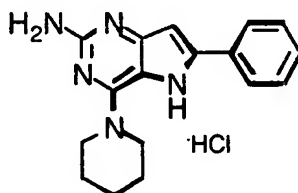
- 5 To a 25-mL, round-bottomed flask was added ethyl 3-amino-5-phenylpyrrole-2-carboxylate (Example 66 (b)) (1.1 g) and MeOH (5 mL). To the reaction flask was added 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea (Aldrich Chemical Company) (1.6 g, 5.5
- 10 mmol), followed by glacial acetic acid (1.43 mL, 25 mmol). The reaction mixture was stirred at room temperature under N₂ for 28 h. A heavy precipitate formed and was collected by filtration, washed with H₂O (3 x 10 mL) and dried in a vacuum oven overnight to
- 15 give 0.71 g (32% from Example 66 (a)) of the title compound as an off-white solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.38 (t, 3, J = 7.00), 1.44 (s, 9), 1.46 (s, 9), 4.38 (q, 2, J = 6.97), 7.31-7.46 (m, 3), 7.76 (d, 2, J = 7.86), 11.06 (br s, 1), 11.25 (s, 1), 11.61 (s,
- 20 1), 11.95 (br s, 1); MS. m/z: 473 (M+1), 471 (M-1).



(d) **2-Amino-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol.**

- To a round-bottomed flask was added a solution of tert-butyl 2-aza-3-[(tert-butoxy)carbonylamino]-3-{[2-(ethoxycarbonyl)-5-phenylpyrrol-3-yl]amino}prop-2-enoate (Example 66 (c)) (0.679 g, 1.44 mmol) in CH₂Cl₂ (8 mL). Trifluoroacetic acid (2 mL) was added, and the reaction mixture was stirred at room temperature under N₂ for 4.5 h. After the solvent was evaporated in
- 25

vacuo, the residue was heated in EtOH (8 mL) and 1N NaOH (4 mL) at reflux for 2 h. The reaction mixture was concentrated in vacuo to ca. 4 mL, and the pH of the resulting suspension was adjusted to pH 6 (pH paper) with 10% HCl. The precipitate that formed was collected by filtration, washed with water and dried in a vacuum oven overnight to give 0.2 g (61%) of the title compound as an off-white solid. ¹H NMR (DMSO-d₆; 500 MHz): δ 5.81 (br s, 1), 6.56 (s, 1), 7.28-7.41 (m, 3), 7.87 (d, 1, J = 7.44), 10.40 (br s, 1), 11.78 (br s, 1); MS m/z: 227 (M+1), 225 (M-1).

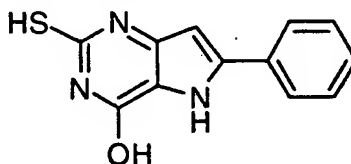


(e) 6-Phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-ylamine Hydrochloride Hydrate.

15 In a round-bottomed flask was added 2-amino-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol (Example 66 (d)) (0.26 g, 1.2 mmol) and phosphorus oxychloride (2.7 mL, 28.8 mmol). The mixture was heated in a 124 °C oil bath for 24 h, then excess POCl₃ was removed in vacuo to afford a brown residue. Ice-cold water was added and the pH of the solution was adjusted to pH 8 (pH paper) by adding aqueous Na₂CO₃. The resulting precipitate was collected by filtration, washed with water and then dried in a vacuum oven at 40 °C to give a brown solid. This material was transferred to a round-bottomed flask and heated with piperidine (0.57 mL, 5.75 mmol) and dioxane (8 mL) in a 110 °C oil bath for 15 h. Most of the solvent was then evaporated in vacuo. Chloroform was added to the residue, and the organic layer was separated, washed with water, dried over Na₂SO₄, and concentrated in vacuo to give a brown

foam. Purification by flash chromatography on silica gel with 100:2:1 CHCl₃:MeOH:Et₃N as eluent afforded 92 mg (27%) of the title compound as a tan solid. The above material (78 mg, 0.27 mmol) was dissolved in a minimal amount of CHCl₃, and HCl (0.6 mL of a 1M soln in ether, 0.6 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min, and the solvent was evaporated in vacuo to give a tan foam. Recrystallization from MeOH/H₂O gave 26 mg (6%) of the title compound as off-white crystals. Mp: >300 °C (dec). ¹H NMR (DMSO-d₆; 500 MHz): δ 1.66-1.67 (m, 6), 3.97 (m, 4), 6.66 (s, 1), 7.32 (br s, 2), 7.45-7.53 (m, 3), 7.87 (d, 2, J = 7.26), 11.53 (br s, 1), 12.51 (br s, 1); MS m/z: 294 (M+1), 292 (M-1). Anal. Calcd for C₁₇H₁₅N₃•HCl•0.2H₂O: C, 61.28%; H, 6.16%; N, 21.02%; Cl, 10.64%. Found: C, 61.28%; H, 6.15%; N, 21.06%; Cl, 10.78%.

Example 67



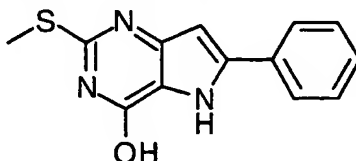
(a) 6-Phenyl-2-sulfanylpyrrolo[3,2-d]pyrimidin-4-ol.

To a solution of ethyl 3-amino-5-phenylpyrrole-2-carboxylate (Example 66 (b)) (4.6 g) in dry benzene (100 mL) was added ethyl isothiocyanatoformate (Aldrich Chemical Company) (2.4 mL, 20 mmol). The reaction mixture was heated to 90 °C for 1 h. A precipitate formed and was filtered, washed with hexane to give 4.6 g of a brown solid. The crude solid was treated with 10 g of potassium hydroxide in water (160 mL), and heated at reflux for 15 h at 100 °C. After cooling to ambient temperature, the pH of the solution was adjusted to pH 5 with 12 M HCl. A

precipitate formed and was collected by filtration.

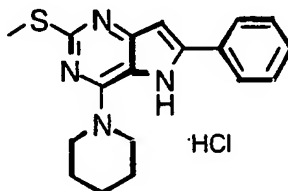
This material was washed with water, and dried in a vacuum oven to give 1.2 g (32% from the tosylate) of the title compound as a brown solid. ¹H NMR (DMSO-d₆;

5 400 MHz): δ 6.40 (s, 1), 7.35-7.54 (m, 3), 7.88 (d, 2, J = 7.44), 12.04 (s, 1), 12.58 (s, 1), 12.68 (br s, 1). MS m/z: 244 (M+1), 242 (M-1).



(b) 2-Methylthio-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol.

10 To a solution of 6-phenyl-2-sulfanylpyrrolo[3,2-d]pyrimidin-4-ol (Example 67(a)) (1.1 g, 4.7 mmol) in acetone (100 mL) was added anhydrous potassium carbonate (0.52 g, 3.7 mmol), followed by iodomethane (0.47 mL, 7.5 mmol). The reaction mixture was stirred
15 at room temperature for 1.5 h. Most of the solvent was evaporated in vacuo and the precipitate formed was collected by filtration, and dried in vacuum oven overnight to give 1.0 g (84%) of the title compound as a tan solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 2.32 (s, 3),
20 6.41 (s, 1), 7.18-7.36 (m, 3), 7.84 (d, 2, J = 7.87), 11.01 (br s, 1). MS m/z: 258 (M+1); 256 (M-1).



(c) 2-Methylthio-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

25 To a suspension of 2-methylthio-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol (Example 67(b)) (1.3 g, 5.0 mmol) in CH₂Cl₂ (50 mL) was added Et₃N (0.84 mL, 6 mmol), followed by methanesulfonyl chloride (Aldrich

Chemical Company) (0.4 mL, 5.3 mmol) at 0°C. The reaction mixture was then warmed to room temperature over 3 h. Piperidine (1.5 mL, 15 mmol) was then added, and the reaction mixture was stirred for 15 h.

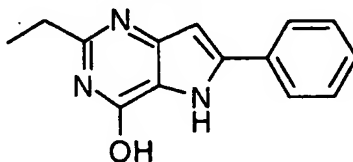
5 A precipitate was then separated from the reaction mixture by filtration, and the filtrate was concentrated in vacuo to give an orange residue. Purification by flash chromatography on silica gel with a gradient of EtOAc(14-20%): hexane(86-80%) as

10 eluant gave 0.1 g (6%) of a white solid. ¹H NMR (CDCl₃; 500 MHz): δ 1.76 (m, 6), 2.60 (s, 3), 3.80 (m, 4), 6.74 (s, 1), 7.38-7.49 (m, 3), 7.64 (d, 2, J = 7.11), 8.04 (br s, 1). The above material (90 mg, 0.28 mmol) was dissolved in minimum amount of CHCl₃,

15 and HCl (0.3 mL of a 1M soln in ether, 0.3 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min, and the solvent was then evaporated in vacuo to give a white foam that was recrystallized from CHCl₃/petroleum ether to give 55 mg

20 (3%) of the title compound as white crystals. Mp: 281-283 °C (dec). ¹H NMR (DMSO-d₆; 500 MHz): δ 1.73 (m, 6), 2.67 (s, 3), 4.05 (m, 4), 6.82 (s, 1), 7.49-7.57 (m, 3), 7.95 (d, 2, J = 7.45), 11.92 (br s, 1). MS m/z: 325 (M+1), 323 (M-1). Anal. Calcd for

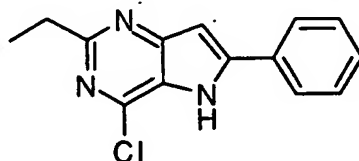
25 C₁₈H₂₀N₄S•HCl•1.8H₂O: C, 54.99%; H, 6.30%; N, 14.25%; Cl, 9.02%. Found: C, 54.99%; H, 5.93%; N, 14.09%; Cl, 9.09%.

Example 68

30

(a) 2-Ethyl-6-phenylpyrrolo[3,2-d]pyrimidine-4-ol.

Dry HCl gas was bubbled through a solution of ethyl 3-amino-5-phenylpyrrole-2-carboxylate (Example 66(b)) (3 g, 13 mmol) in propionitrile (Aldrich Chemical Company) (100 mL) at room temperature for 1.5 h. The reaction mixture was then capped and stirred at room temperature for 18 h. The solvent was evaporated in vacuo to give a solid that was dissolved in EtOH (80 mL) and 6% aqueous NaOH (50 mL) and the resulting solution was heated at reflux for 6 h. The solvent was concentrated in vacuo, and the resulting suspension was acidified with 12 M HCl to pH 5. Filtration of the reaction mixture lead to the isolation of a precipitate which was dried in a vacuum oven to give 2.6 g (85%) of the title compound as a tan solid. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.22 (t, 3, J = 7.54), 2.60 (q, 2, J = 7.52), 6.83 (s, 1), 7.32-7.42 (m, 3), 7.92 (d, 2, J = 7.81), 11.7 (br s, 1), 12.1 (br s, 1). MS m/z: 240 (M+1), 238 (M-1).

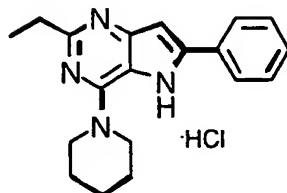


(b) 4-Chloro-2-ethyl-6-phenylpyrrolo[3,2-d]pyrimidine.

A mixture of 2-ethyl-6-phenylpyrrolo[3,2-d]pyrimidine-4-ol (Example 68 (a)) (0.6 g, 2.5 mmol) and POCl₃ (5.8 mL, 62 mmol) was heated at 120 °C for 21 h. POCl₃ was removed in vacuo to give a dark-red residue. Ice-water was added, and the pH of the reaction mixture was adjusted to pH 8 by the addition of aq NH₃ at 0 °C. The resulting mixture was extracted three times with EtOAc. Combined organic layer were washed with brine, dried over Na₂SO₄, concentrated in vacuo and dried in a vacuum oven overnight to give 0.31 g (47%) of the title compound as a tan solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.41 (t, 3, J = 7.57), 3.04 (q,

139

2, $J = 7.60$), 6.95 (s, 1), 7.45-7.54 (m, 3), 7.76 (d, 2, $J = 8.15$), 8.94 (br s, 1). MS m/z : 258, 260 (M+1); 256, 258 (M-1).



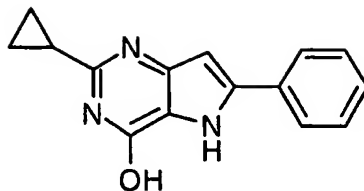
5 (c) **2-Ethyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.**

To a 25-mL, round-bottomed flask were added 4-chloro-2-ethyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 68 (b)) (0.31 g, 1.2 mmol) and piperidine
10 (0.59 mL, 5.9 mmol), followed by addition of a solution of potassium carbonate (1.63 g, 11.8 mmol) in water (8 mL). The reaction mixture was stirred at 120 °C for 4 hr, cooled to room temperature and filtered. The precipitate was washed with water and hexane and
15 dried in a vacuum oven to give 0.308 g (85%) of a tan solid. The above material (234 mg, 0.76 mmol) was dissolved in minimum amount of CHCl_3 , and HCl (0.76 mL of a 1M soln in ether, 0.76 mmol) was added dropwise. After stirring for 20 min at room temperature, the
20 solution was concentrated in vacuo to give a tan foam which was recrystallized from MeOH to give 114 mg (28%) of the title compound as light-tan crystals. Mp: 286-288 °C (dec). ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.32 (t, 3, $J = 7.53$), 1.72 (m, 6), 2.87 (q, 2, $J =$
25 7.51), 4.08-4.09 (m, 4), 6.90 (s, 1), 7.51-7.57 (m, 3), 7.96 (d, 2, $J = 7.36$), 12.01 (br s, 1), 14.36 (br s, 1). MS m/z : 307 (M+1), 305 (M-1). Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_4 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 63.24; H, 6.98; N, 15.52; Cl, 9.82. Found: C, 63.25; H, 6.99; N, 15.50, Cl, 10.10.

30

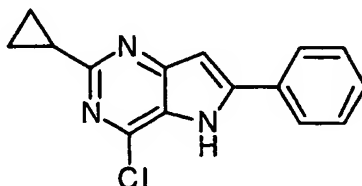
Example 69

140



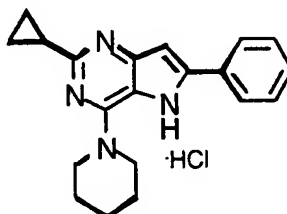
(a) 2-Cyclopropyl-6-phenylpyrrolo[3,2-d]pyrimidine-4-ol.

Dry HCl gas was bubbled through a suspension of
5 ethyl 3-amino-5-phenylpyrrole-2-carboxylate (Example
66 (b)) (2.48 g, 8.84 mmol) in cyclopropylcyanide
(Aldrich Chemical Company) (75 g) at room temperature
for 1.5 h. The reaction mixture was capped and
stirred at room temperature overnight. The solvent
10 was evaporated *in vacuo* to give a dark-red residue,
which was dissolved in EtOH (70 mL) and 6% aqueous
sodium hydroxide (50 mL). The reaction mixture was
heated at reflux for 6 h. The solvent was evaporated
in vacuo and the resulting suspension was found to be
15 pH 6. The aqueous layer was removed and the brownish
residue was dissolved in toluene and evaporated. The
residue was again dissolved in toluene and evaporated
to give a brown oil. The crude material was purified by
flash chromatography on silica gel with 100:3
20 CHCl₃:MeOH as eluant to give 0.945 g (43%, 3 steps from
tosylate) of the title compound as a tan solid. ¹H NMR
(DMSO-d₆; 500 MHz) δ 0.61-0.64 (m, 2), 0.93-0.95 (m,
1), 0.96-1.00 (m, 1), 1.93-1.98 (m, 1), 6.72 (s, 1),
7.31-7.44 (m, 3), 7.95 (d, 2, J = 7.63), 11.99 (br s,
25 1), 12.21 (br s, 1); MS *m/z*: 252 (M+1), 250 (M-1).



(b) 4-Chloro-2-cyclopropyl-6-phenylpyrrolo[3,2-d]pyrimidine.

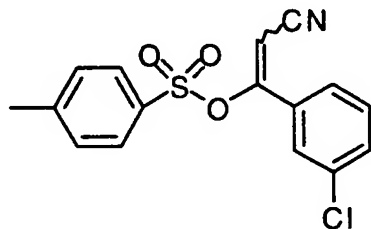
A mixture of 2-cyclopropyl-6-phenylpyrrolo[3,2-d]pyrimidine-4-ol (Example 69 (a)) (0.914 g, 3.64 mmol) and phosphorus oxychloride (Aldrich Chemical Company) (8.5 mL, 91 mmol) was heated at 120 °C for 24 h. The excess POCl₃ was removed under reduced pressure, and toluene was added. The toluene was evaporated to give a brown residue. The residue was diluted with ice-water and neutralized under stirring and cooling with ammonia water to pH 6. The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo, and dried in vacuum oven overnight to give 0.462 g (47%) of the title compound as a brown solid. ¹H NMR (CDCl₃; 500 MHz): δ 1.01-1.07 (m, 2), 1.16-1.20 (m, 1), 1.24-1.27 (m, 1), 2.28-2.36 (m, 1), 6.88 (s, 1), 7.45-7.53 (m, 3), 7.74 (d, 2, J = 7.31), 8.69 (br s, 1); MS m/z: 270, 272 (M+1); 268, 270 (M-1).



(c) 2-Cyclopropyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.

To a 25-mL, round-bottomed flask were added 4-chloro-2-cyclopropyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 69 (b)) (0.311 g, 1.15 mmol) and piperidine (0.57 mL, 5.77 mmol), followed by addition of a solution of potassium carbonate (1.59 g, 11.5 mmol) in 8 mL of H₂O. The reaction mixture was stirred at 120 °C for 4 h. After cooling to room temperature, a precipitate formed and was collected by filtration. The solids were washed with H₂O and hexane, and dried in a vacuum oven to give 0.334 g of a brown solid.

This material was purified by flash chromatography on silica gel with 1:1 EtOAc:hexane as eluant to give 0.078 g of a tan solid. The insoluble material on top of the column was isolated to give an additional 0.11 g of product as an off-white solid (total yield: 51%). The purified material (67 mg, 0.21 mmol) was dissolved in minimum amount of CHCl_3 . Ethereal hydrogen chloride (1N, 0.21 mL, 0.21 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min. Solvent was then evaporated *in vacuo* to give a tan foam, which was recrystallized from MeOH/ H_2O to give 20 mg of the title compound as white needles. Mp: 285.4-286.0 °C (dec). ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.14-1.21 (m, 4), 1.67-1.71 (m, 6), 2.20-2.24 (m, 1), 3.98-3.99 (m, 4), 6.88 (s, 1), 7.49-7.65 (m, 3), 7.95 (d, 2, $J = 7.78$), 11.95 (br s, 1), 14.51 (br s, 1); MS m/z : 319 ($M+1$), 317 ($M-1$). Calcd for $\text{C}_{20}\text{H}_{23}\text{ClN}_4\cdot\text{H}_2\text{O}$: C, 64.42; H, 6.76; N, 15.02; Cl, 9.51. Found: C, 64.40; H, 6.75; N, 14.93, Cl, 9.41.

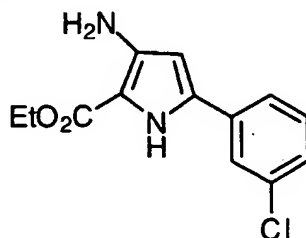


Example 70

(a) 1-(3-Chlorophenyl)-2-cyanovinyl 4-methylbenzenesulfonate.

To a 100-mL, round-bottomed flask were added 3-chlorobenzoyl acetonitrile (Maybridge Chemical Company) (5.13 g, 28.5 mmol), *p*-toluenesulfonyl chloride (Aldrich Chemical Company) (6.53 g, 34.3 mmol) and CH_2Cl_2 (50 mL). To the above solution was added Et_3N (6 mL, 42.8 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h, then at room

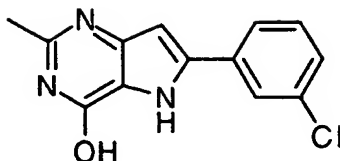
temperature for 22 h. The cloudy reaction mixture was partitioned between H₂O and CH₂Cl₂. The organic layer was separated, washed three times with H₂O, dried over Na₂SO₄, and concentrated in vacuo to give a dark-red residue. This material was purified by flash chromatography on silica gel with 1:10 of EtOAc:hexane as eluent to give 8.79 g (92%) of the title compound as a yellow solid. ¹H NMR (CDCl₃; 400 MHz): δ 2.45, 2.47 (d, 3), 5.60, 5.62 (d, 1), 7.32-7.48 (m, 6), 7.74 (d, 1, J = 8.37), 7.88 (d, 1, J = 8.40). MS m/z: 351 (base peak), 332 (M-1).



(b) Ethyl 3-amino-5-(3-chlorophenyl)pyrrole-2-carboxylate.

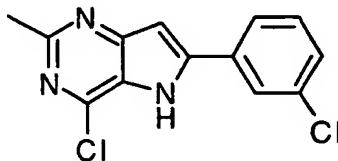
Sodium ethoxide was prepared fresh from Na (1.77 g, 77.1 mmol) and EtOH (30 mL). To the above solution was added a solution of 1-(3-chlorophenyl)-2-cyanovinyl 4-methylbenzenesulfonate (Example 70 (a)) (8.56 g, 25.7 mmol), aminodiethyl malonate hydrochloride (Aldrich Chemical Company) (5.43 g, 25.7 mmol) in EtOH (70 mL) through a dropping funnel. After the addition was complete, the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated in vacuo and the residue was partitioned between EtOAc and H₂O. The organic layer was separated, dried over Na₂SO₄, and concentrated in vacuo to give 5.926 g of a brown solid (This material was used directly in the following step without further purification).

144



(c) 6-(3-Chlorophenyl)-2-methylpyrrolo[3,2-d]pyrimidine-4-ol.

Dry HCl gas was bubbled through a solution of
5 ethyl 3-amino-5-(3-chlorophenyl)pyrrole-2-carboxylate
(Example 70 (b)) (3.5 g) in 120 mL of acetonitrile at
room temperature for 1.5 h. The reaction mixture was
capped, and stirred at room temperature overnight.
The solvent was evaporated in vacuo to give a solid,
10 which was dissolved in EtOH (70 mL) and 6% aqueous
NaOH (23 mL). The reaction mixture was heated at
reflux for 6 h. The precipitate that formed was
filtered, and dried in a vacuum oven to give 1.17 g of
a tan solid as pure product. The filtrate was
15 concentrated and the resulting suspension was filtered
to give a viscous solid. This material was purified
by flash chromatography on silica gel with 100:5 of
CHCl₃:MeOH as eluent to give 0.46 g (41% from the
tosylate (70(a)) of the title compound as a tan solid.
20 ¹H NMR (DMSO-d₆; 500 MHz): δ 2.31 (s, 3), 6.86 (s, 1),
7.38 (d, 1, J = 7.38), 7.45 (t, 1, J = 7.89), 7.90 (d,
1, J = 7.82), 8.06 (s, 1), 11.81 (br s, 1), 12.41 (br
s, 1); MS m/z: 260, 262 (M+1), 258, 260 (M-1).

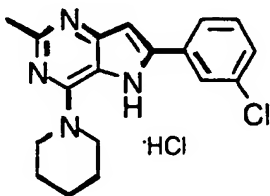


(d) 4-Chloro-6-(3-chlorophenyl)-2-methylpyrrolo[3,2-d]pyrimidine.

A mixture of 6-(3-chlorophenyl)-2-methylpyrrolo
[3,2-d]pyrimidine-4-ol (Example 70 (c)) (1.55 g, 5.97
mmol) and phosphorus oxychloride (14 mL, 149 mmol) was

heated at 120 °C for 24 h. The excess POCl₃ was removed under reduced pressure to give a dark-red residue. The residue was diluted with ice-water and neutralized under stirring and cooling with ammonia water to pH 5.

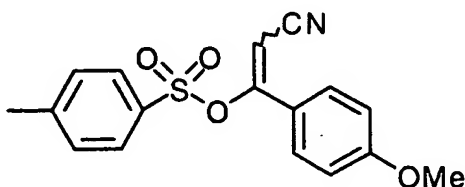
5 The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 1.42 g (85%) of the title compound as a brown solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 2.79 (s, 3), 6.92 (s, 1), 7.43-7.46 (m, 2), 7.66 (d, 1, J = 6.5), 7.74 (s, 1), 9.10 (br s, 1). MS *m/z*: 278 (M+1); 276 (M-1).



(e) 6-(3-Chlorophenyl)-2-methyl-4-piperidylpyrrolo [3,2-d]pyrimidine Hydrochloride Monohydrate.

15 To a 25-mL, round-bottomed flask were added 4-chloro-6-(3-chlorophenyl)-2-methylpyrrolo[3,2-d]pyrimidine (Example 70 (d)) (0.5 g, 1.8 mmol) and piperidine (Aldrich Chemical Company) (0.89 mL, 9 mmol), followed by addition of a solution of potassium carbonate (2.49 g, 18 mmol) in 10 mL of H₂O. The
20 reaction mixture was stirred at 120 °C for 4 h. The mixture was allowed to cool to roomtemperature and was extracted with CH₂Cl₂. The organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo*
25 to give a brown solid. This material was purified by flash chromatography on silica gel with 1:1 of EtOAc:hexane as eluent to give 0.42 g (71%) of a beige solid. A portion of this material (345 mg, 1.06 mmol) was dissolved in minimum amount of CHCl₃, and ethereal
30 hydrogen chloride (1N, 1.1 mL, 1.1 mmol) was added dropwise. The mixture was stirred at room temperature

for 20 min. Solvent was then evaporated in vacuo to give a light-yellow foam, which was recrystallized from MeOH to give 170 mg of the title compound as white crystals. MP: 244.5-246 °C (dec). ¹H NMR (DMSO-
5 d₆; 500 MHz): δ 1.72 (m, 6), 2.57 (s, 3), 4.06-4.07 (m, 4), 7.00 (s, 1), 7.56-7.58 (m, 2), 7.93-7.94 (m, 1), 8.10 (s, 1), 11.99 (br s, 1), 14.31 (br s, 1). MS m/z: 327, 329 (M+1), 325, 327 (M-1). Calcd for C₁₈H₂₀Cl₂N₄H₂O: C, 56.70; H, 5.82; N, 14.69; Cl, 18.60.
10 Found: C, 56.75; H, 5.81; N, 14.62, Cl, 18.47.



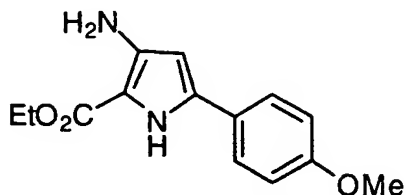
Example 71

(a) 2-Cyano-1-(4-methoxyphenyl)vinyl 4-methylbenzene sulfonate.
15

To a 100-mL, round-bottomed flask were added 4-methoxybenzoyl acetonitrile (Maybridge Chemical Company) (5 g, 28.5 mmol), *p*-toluenesulfonyl chloride (Aldrich Chemical Company) (6.53 g, 34.3 mmol) and
20 CH₂Cl₂ (50 mL). To the above solution was then added Et₃N (6 mL, 42.8 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h, and at room temperature for 48 h. The cloudy reaction mixture was partitioned between H₂O and CH₂Cl₂. The organic layer was separated,
25 washed three times with water, dried over Na₂SO₄, and concentrated in vacuo to give a dark-red residue. This material was purified by flash chromatography on silica gel with 1:10 to 1:8 of EtOAc:hexane as eluent to give 4.73 g (50%) of the title compound as a yellow
30 solid. ¹H NMR (CDCl₃; 400 MHz): δ 2.47 (s, 3), 3.86 (s, 3), 5.45 (s, 1), 6.91 (d, 2, J = 8.9), 7.38 (d, 2,

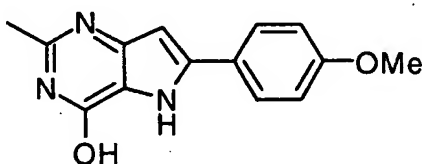
147

$J = 8.22$), 7.55 (d, 2, $J = 8.95$), 7.92 (d, 2, $J = 8.34$) (for one isomer). MS m/z : 330 (M+1), 328 (M-1).



5 **(b) Ethyl 3-amino-5-(4-methoxyphenyl)pyrrole-2-carboxylate.**

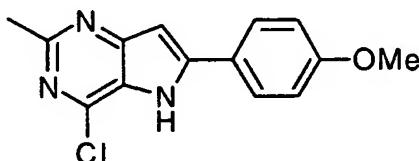
Sodium ethoxide was prepared fresh from Na (0.97 g, 42.3 mmol) and EtOH (30 mL). To the above solution was added a solution of 2-cyano-1-(4-methoxyphenyl) vinyl 4-methylbenzenesulfonate (Example 71(a)) (4.64 g, 14.1 mmol), aminodiethyl malonate hydrochloride (Aldrich Chemical Company) (2.98 g, 14.1 mmol) in EtOH (40 mL) and THF (30 mL) through a dropping funnel. After the addition was complete, the reaction mixture was stirred at room temperature for 21 h. The solvent was evaporated in vacuo and the residue was partitioned between EtOAc and H₂O. The organic layer was separated, dried over Na₂SO₄, and concentrated in vacuo to give 2.98 g of an orange solid (This material was used directly in the following step without further purification).



(c) 6-(4-Methoxyphenyl)-2-methylpyrrolo[3,2-d]pyrimidine-4-ol.

Dry HCl gas was bubbled through a solution of ethyl 3-amino-5-(4-methoxyphenyl)pyrrole-2-carboxylate (Example 71(b)) (2.75 g) in 90 mL of acetonitrile at room temperature for 1.5 h. The reaction mixture was then capped and stirred at room temperature overnight. The solvent was evaporated in vacuo to give a solid,

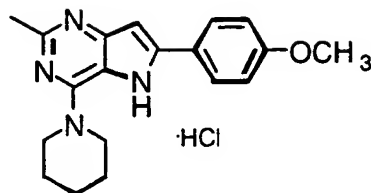
which was dissolved in EtOH (50 mL) and 6% aqueous NaOH (16 mL). The reaction mixture was heated at reflux for 6 h. The EtOH was evaporated *in vacuo* to give a suspension. The precipitate that formed was
5 filtered, washed with H₂O, and dried in a vacuum oven to give 1.69 g of a brown solid (This material was used directly in the following step without further purification).



10 **(d) 1-(4-Chloro-2-methylpyrrolo[4,5-d]pyrimidin-6-yl)-4-methoxybenzene.**

A mixture of 6-(4-methoxyphenyl)-2-methylpyrrolo [3,2-d]pyrimidine-4-ol (Example 71(c)) (1.50 g, 5.89 mmol) and phosphorus oxychloride (14 mL, 149 mmol) was
15 heated at 120 °C for 24 h. The excess POCl₃ was removed under reduced pressure to give a dark-red residue. This material was diluted with ice-water and neutralized under stirring and cooling with ammonia water to pH 7. The resulting mixture was extracted
20 three times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to give a viscous oil. This material was purified by flash chromatography on silica gel with 1:4 to 1:1 of EtOAc:hexane as eluent
25 to give 0.334 g (11% from the tosylate) of the title compound as a tan solid. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 2.78 (s, 3), 3.89 (s, 3), 6.82 (s, 1), 7.04 (d, 2, J = 8.82), 7.70 (d, 2, J = 8.74), 8.68 (br s, 1). MS *m/z*: 274 (M+1); 272 (M-1).

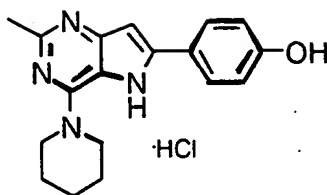
149



(e) 4-Methoxy-1-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzene Hydrochloride Monohydrate.

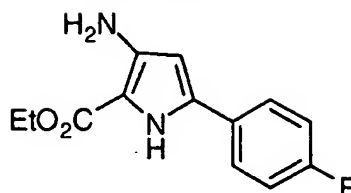
To a 15-mL, round-bottomed flask was added 1-(4-chloro-2-methylpyrrolo[4,5-d]pyrimidin-6-yl)-4-methoxybenzene (Example 71(d)) (0.3 g, 1.1 mmol) and piperidine (Aldrich Chemical Company) (0.54 mL, 5.5 mmol), followed by the addition of a solution of potassium carbonate (0.759 g, 5.5 mmol) in H₂O (5 mL). The reaction mixture was stirred at 120 °C for 4 h. The precipitate that formed was collected by filtration, washed with H₂O and hexane, and dried in a vacuum oven to give 0.332 g (94%) of a tan solid. The above material (186 mg, 0.58 mmol) was dissolved in a minimum amount of CHCl₃, and ethereal hydrogen chloride (1N, 0.6 mL, 0.6 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min. The solvent was then evaporated in vacuo to give a tan solid, which was recrystallized from MeOH to give 77 mg of the title compound as light-tan crystals. MP: 267.5- 268 °C (dec). ¹H NMR (DMSO-d₆; 500 MHz): δ 1.63-1.72 (m, 6), 2.54 (s, 3), 3.84 (s, 3), 4.00 (m, 4), 6.78 (s, 1), 7.10 (d, 2, J = 8.67), 7.90 (d, 2, J = 8.67), 8.56 (br s, 1), 11.73 (br s, 1). Calcd for C₁₉H₂₃ClN₄O·H₂O: C, 60.55; H, 6.69; N, 14.87; Cl, 9.41. Found: C, 60.77; H, 6.62; N, 14.84, Cl, 9.25.

150

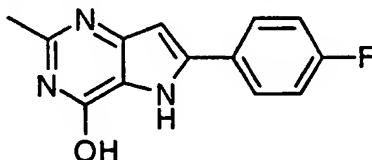
**Example 72****4-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenol Hydrochloride Monohydrate.**

5 The suspension of 4-methoxy-1-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzene (Example 71(e)) (0.138 g, 0.43 mmol) in anhydrous CH_2Cl_2 (12 mL) was cooled to -70°C under nitrogen atmosphere. Boron tribromide (Aldrich Chemical Company) (0.41 mL, 4.3 mmol) in CH_2Cl_2 (4 mL) was added dropwise. The reaction mixture was stirred at -70°C to room temperature for 16 h. The solution was poured into 40 mL of ice-water. The resulting mixture was basified with Et_3N to pH 10 and stirred for a period of 3 h. The precipitate that formed was collected by filtration, washed with H_2O , and dried in a vacuum oven to give 78.7 mg (60%) of a tan solid. A portion of this material (74 mg, 0.24 mmol) was dissolved in minimum amount of CHCl_3 , and ethereal hydrogen chloride (1N, 0.26 mL, 0.26 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min. Solvent was then evaporated *in vacuo* to give a brown solid, which was recrystallized from $\text{MeOH}/\text{H}_2\text{O}$ to give 25 mg of the title compound as light-tan crystals. MP: $> 300^\circ\text{C}$ (dec). ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.70 (m, 6), 2.55 (s, 3), 4.03 (m, 4), 6.73 (s, 1), 6.93 (d, 2, $J = 8.54$), 7.79 (d, 2, $J = 8.54$), 10.04 (s, 1), 11.75 (br s, 1), 14.15 (br s, 1); MS m/z : 309 ($M+1$), 307 ($M-1$). Calcd for $\text{C}_{18}\text{H}_{21}\text{ClN}_4\text{O}\cdot\text{H}_2\text{O}$: C, 59.58; H, 6.39; N, 15.44. Found: C, 59.13; H, 6.33; N, 15.20.

151

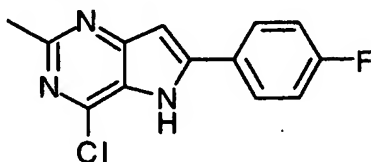
Example 73**(a) Ethyl 3-amino-5-(4-fluorophenyl)pyrrole-2-carboxylate.**

5 Sodium ethoxide was prepared fresh from Na (2.66 g, 116 mmol) and EtOH (40 mL). To this solution was added a solution of 3-chloro-3-(4-fluorophenyl)acrylonitrile (Maybridge Chemical Company) (7.00 g, 38.5 mmol), aminodiethyl malonate hydrochloride (Aldrich
10 Chemical Company) (8.16 g, 38.5 mmol) in EtOH (110 mL) through an addition funnel. After the addition was complete, the reaction mixture was stirred at room temperature for 21 h. The solvent was evaporated in vacuo and the residue was partitioned between EtOAc
15 and H₂O. The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo to give 11.63 g of a dark-red solid (This material was used directly in the following step without further purification).

**20 (b) 6-(4-Fluorophenyl)-2-methylpyrrolo[3,2-d]pyrimidine-4-ol.**

Dry HCl gas was bubbled through a solution of ethyl 3-amino-5-(4-fluorophenyl)pyrrole-2-carboxylate (Example 73(a)) (8.78 g) in 250 mL of acetonitrile at
25 room temperature for 1.5 h. The reaction mixture was then capped and stirred at room temperature overnight. The solvent was evaporated in vacuo to give a brownish residue, which was dissolved in EtOH (150 mL) and 6% aqueous NaOH (50 mL). The reaction mixture was heated

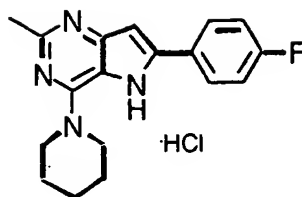
at reflux for 6 h. The precipitate that formed was filtered, dried in a vacuum oven to give 1.25 g of a tan solid as a pure product. The filtrate was concentrated and the resulting suspension was filtered to give a viscous solid, which was purified by flash chromatography on silica gel with 100:5 of CHCl₃: MeOH as eluent to give 0.604 g (total yield 26% from the chloride) of the title compound as a tan solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 2.31 (s, 3), 6.72 (s, 1), 7.26-7.28 (m, 2), 7.96-7.97 (m, 2), 11.76 (br s, 1), 12.24 (br s, 1). MS m/z: 244 (M+1), 242 (M-1).



(c) 4-Chloro-6-(4-fluorophenyl)-2-methylpyrrolo[3,2-d]pyrimidine.

A mixture of 6-(4-fluorophenyl)-2-methylpyrrolo[3,2-d]pyrimidine-4-ol (Example 73(b)) (1.84 g, 7.58 mmol) and phosphorus oxychloride (18 mL, 189 mmol) was heated at 120 °C for 24 h. The excess POCl₃ was removed under reduced pressure to give a dark-brown residue. This material was diluted with ice-water and neutralized under stirring and cooling with ammonia water to pH 8. The resulting mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give 1.22 g (62%) of product as a brown solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 2.79 (s, 3), 6.87 (s, 1), 7.19-7.23 (m, 2), 7.74-7.78 (m, 2), 9.17 (br s, 1). MS m/z: 262, 264 (M+1); 260, 262 (M-1).

153

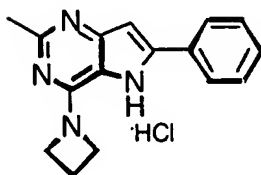


(d) 6-(4-Fluorophenyl)-2-methyl-4-piperidylpyrrolo [3,2-d]pyrimidine Hydrochloride.

To a 25-mL, round-bottomed flask were added 4-chloro-6-(4-fluorophenyl)-2-methylpyrrolo[3,2-d]pyrimidine (Example 73(c)) (0.5 g, 1.9 mmol) and piperidine (Aldrich Chemical Company) (0.95 mL, 9.6 mmol), followed by addition of a solution of potassium carbonate (2.64 g, 19 mmol) in 10 mL of water. The reaction mixture was stirred at 120 °C for 4 h. After cooling to room temperature, CH₂Cl₂ was added. The precipitate that formed was collected by filtration, and dried in a vacuum oven to give 0.168 g of an off-white solid as pure product. The filtrate was extracted with CH₂Cl₂, the organic layer was separated, dried over Na₂SO₄, and concentrated in vacuo to give a brown solid. This material was purified by flash chromatography on silica gel with 1:1 of EtOAc:hexane as eluent to give 0.196 g (61% total yield) of an off-white solid. This material (196 mg, 0.63 mmol) was dissolved in minimum amount of CHCl₃, and ethereal hydrogen chloride (1N, 0.65 mL, 0.65 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min. The solvent was evaporated in vacuo to give an off-white solid, which was recrystallized from MeOH to give 67 mg of the title compound as off-white crystals. MP: 287- 289 °C (dec). ¹H NMR (DMSO-d₆; 500 MHz): δ 1.87-1.88 (m, 6), 2.74 (s, 3), 4.22-4.23 (m, 4), 7.05 (s, 1), 7.55-7.59 (m, 2), 8.19-8.22 (m, 2), 12.18 (br s, 1), 14.63 (br s, 1). MS m/z: 311 (M+1), 309 (M-1). Calcd for C₁₈H₂₀ClFN₄·H₂O: C, 59.26; H, 6.08;

154

N, 15.36; Cl, 9.72. Found: C, 59.30; H, 6.10; N, 15.22, Cl, 9.67.

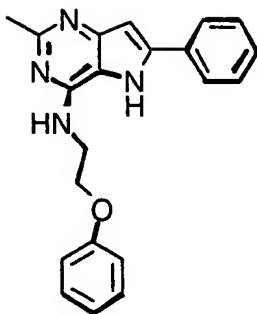
Example 74

5

4-Azetidinyl-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

This compound was prepared according to the method described in Example 73(d), by employing 2-methyl-4-chloro-6-phenyl-5H-pyrrolo[3,2-d]pyrimidine (Example 1(e)) (0.3 mg, 1.23 mmol), azetidine (Aldrich Chemical Company) (0.41 mL, 6.16 mmol) and potassium carbonate (1.7 g, 12.3 mmol) in H₂O (8 mL) to give 0.322 g (99%) of an off-white solid. A portion of this material (298 mg, 1.13 mmol) was dissolved in minimum amount of CHCl₃ and MeOH, and ethereal hydrogen chloride (1N, 1.2 mL, 1.2 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min. The precipitate that formed was filtered, recrystallized from MeOH/H₂O to give 190 mg of the title compound as white crystals. MP: >300 °C (dec). ¹H NMR (DMSO-d₆; 500 MHz): δ 2.48-2.52 (m, 2), 2.55 (s, 3), 4.46-4.63 (m, 4), 6.88 (s, 1), 7.49-7.57 (m, 3), 7.95 (d, 2, J = 7.69), 11.78 (br s, 1), 14.32 (br s, 1). MS m/z: 265 (M+1), 263 (M-1). Calcd for C₁₆H₁₇ClN₄·H₂O: C, 60.28; H, 6.01; N, 17.57; Cl, 11.12. Found: C, 60.23; H, 5.96; N, 17.54, Cl, 11.18.

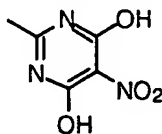
155

**Example 75**

(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(2-phenoxyethyl)amine Hydrochloride.

5 This compound was prepared according to the method described in Example 2, by employing 2-methyl-4-chloro-6-phenyl-5H-pyrrolo[3,2-d]pyrimidine (Example 1(e)) (100 mg, 0.41 mmol), 2-phenoxyethylamine (Lancaster Synthesis Ltd.) (0.28 g, 2.05 mmol) and
10 potassium carbonate (0.567 g, 4.1 mmol) in H₂O (2.5 mL) to give 30.7 mg (22%) of the title compound as white crystals. MP: 266.9-267.4 °C (dec). ¹H NMR (DMSO-d₆; 400 MHz): δ 2.43 (s, 3), 3.91-3.93 (m, 2), 4.22 (t, 2, J = 5.3), 6.74 (s, 1), 6.93-7.07 (m, 4), 7.29-7.40 (m, 3), 7.49-7.52 (m, 2), 7.79 (d, 2, J = 7.79), 11.33 (br
15 s, 1). MS m/z: 345 (M+1), 343 (M-1). Anal. Calcd for C₁₉H₂₄N₄O: C, 70.34; H, 7.46; N, 17.27. Found: C, 70.14; H, 7.35; N, 17.13.

20

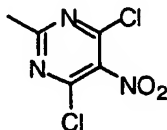
Example 76

(a) 2-Methyl-4,6-dihydroxy-5-nitropyrimidine.

To a three-necked, round-bottomed flask equipped with an addition funnel, condensor, internal
25 temperature probe and mechanical stirrer was added trifluoroacetic acid (Aldrich Chemical Company) (120

156

mL, 710 mmol) and powdered 2-methyl-4,6-dihydroxy pyrimidine (Aldrich Chemical Company) (20 g, 160 mmol). The suspension was stirred under a N₂ atmosphere for 15 min to allow complete dissolution of the solids. Nitric acid (9.7 mL, 210 mmol, 90 % aq soln) was added over 25 min while maintaining the internal temperature between 13-21 °C by cooling the reaction flask in an ice bath. Stirring was continued for 12 h at room temperature. Water (100 mL) was added, and the resulting precipitate was collected by filtration and washed with H₂O. Recrystallization from H₂O followed by drying in the vacuum oven provided 20 g (68 %) of the title compound as a white crystalline solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 3.9 (s, 3). ¹³C NMR (DMSO-d₆; 100.6 MHz): δ 17.94, 118.0, 155.7, 161.7. MS m/z.: 170 (M-1).



(b) 2-Methyl-4,6-dichloro-5-nitropyrimidine.

To a round-bottomed flask equipped with a Dean-Stark trap, reflux condensor, pressure-equalized addition funnel, magnetic stirrer, heating mantel and internal temperature probe was added 2-methyl-4,6-dihydroxy-5-nitropyrimidine (Example 76(a)) (2.0 g, 11 mmol) and toluene (16 mL). The Dean-Stark trap was filled with toluene (12 mL). For 3 h, the reaction mixture was heated at reflux during which time water collected in the Dean-Stark trap. Heat was removed from the reaction vessel, and after 20 min, diisopropylethylamine (Aldrich Chemical Company) (2.8 mL, 16 mmol) was poured into the reaction mixture through the reflux condensor. The reaction mixture was heated at reflux again, and POCl₃ (Aldrich Chemical Company) (7 mL, 74 mmol) was added through the

157

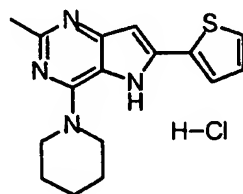
addition funnel at such a rate as to maintain the internal temperature below 113 °C (8 min). Vigorous bubbling was observed during the addition of POCl₃. Following this addition, the reaction mixture was

5 heated for an additional 3 h at reflux. Heat was then removed from the flask, and the reaction was stirred at room temperature for 18 h. The reaction mixture was then poured onto ice-water (100 mL), shaken in a separatory funnel, and filtered through a pad of

10 Celite. The organic layer was collected from the filtrate, and the aqueous layer was extracted twice with ether. All organic fractions were combined, dried over Na₂SO₄, and concentrated in vacuo. Heptane was added to the residue, the contents were filtered

15 through a pad of Celite, and concentrated in vacuo to give the title compound (1.1 g, 49 %) as a brown rod-like crystals in sufficient purity for the next step.

¹H NMR (DMSO-*d*₆; 400 MHz): δ 2.5 (s, 3). ¹³C NMR (DMSO-*d*₆; 100.6 MHz): δ 27.04, 127.0, 153.6, 170.8.



20

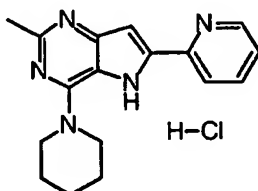
(c) 2-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)thiophene Hydrochloride.

Using the method described in Example 30 by employing 2-(1-pyrrolidinylvinyl)thiophene (freshly prepared before use) (2.39 g, 13.4 mmol), 2-methyl-

25 4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.76 g, 13.4 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (2.3 mL, 13.4 mmol), piperidine (2.1 mL, 21.4 mmol), NEt₃ (Aldrich Chemical Company) (2.0

30 mL) and SnCl₄ (40 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica

gel with 95:5 CHCl₃:MeOH as elutant to give 540 mg (14%) of the free base as a cream colored solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.65 (s, 6), 2.41 (s, 3), 3.30 (s, 2), 3.71 (br s, 2), 6.49 (br s, 1), 7.14 (br s, 1), 7.62 (br s, 1), 11.09 (s, 1). MS m/z : 299 (M+1). To a solution of 2-(2-methyl-4-piperidyl pyrrolo[4,5-d]pyrimidin-6-yl)thiophene (0.54 g, 1.81 mmol) in 5:1 EtOAc: MeOH (30 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.80 mL, 1.80 mmol). The precipitate was collected by filtration, washed with EtOAc (2 x 10 mL), ether (3 x 15 mL) and dried under vacuum to give 550 mg (92%) of the title compound as a tan colored solid. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.71 (s, 6), 2.56 (s, 3), 4.04 (br s, 4), 6.70 (s, 1), 7.26 (t, 1, J = 4.2), 7.80 (d, 1, J = 5.0), 7.89 (d, 1, J = 3.0), 12.15 (s, 1), 14.44 (s, 1). MS m/z : 299 (M+1). Anal. Calcd for C₁₅H₁₈N₄S•HCl: C, 57.39; H, 5.72; N, 16.73; Cl, 10.59. Found C, 57.25; H, 5.75; N, 16.60; Cl, 10.73.

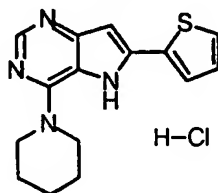


Example 77

2-Methyl-4-piperidyl-6-(2-pyridyl)pyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing 2-(1-pyrrolidinylvinyl)-2-pyridine (freshly prepared before use) (2.20 g, 12.6 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.61 g, 12.6 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (2.2 mL, 12.6 mmol), piperidine (2.0 mL, 20.2 mmol), NEt₃ (Aldrich Chemical Company) (2.0

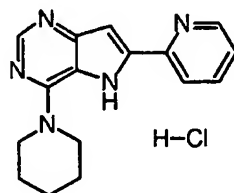
mL) and SnCl_2 (Aldrich Chemical Company) (38 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl_3 :MeOH as elutant to give 650 mg (18%) of the free base as a beige colored solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.66 (s, 6), 2.42 (s, 3), 3.74 (s, 4), 7.01 (br s, 1), 7.37 (br s, 1), 7.90 (br s, 1), 8.08 (d, 1, $J = 7.9$), 8.67 (br s, 1), 11.18 (s, 1). MS m/z : 294 (M+1). To a solution of 2-methyl-4-piperidyl-6-(2-pyridyl)pyrrolo [3,2-d]pyrimidine (0.65 g, 2.22 mmol) in EtOAc (30 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (2.20 mL, 2.22 mmol). The precipitate was collected by filtration, washed with EtOAc (2 x 10 mL), ether (3 x 15 mL) and dried under vacuum to give 621 mg (85%) of the title compound as a brown colored solid. Mp: $>280^\circ\text{C}$. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.72 (s, 6), 2.58 (s, 3), 4.06 (br s, 4), 7.16 (s, 1), 7.51 (dd, 1, $J = 7.4, 7.4$), 8.01 (dt, 1, $J = 1.4, 7.6$), 8.24 (d, 1, $J = 7.9$), 8.76 (d, 1, $J = 4.4$), 12.19 (s, 1), 14.36 (s, 1). MS m/z : 294 (M+1). Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{N}_5 \cdot 1.2\text{HCl} \cdot 0.4\text{H}_2\text{O}$: C, 59.18; H, 6.14; N, 20.30; Cl, 12.53. Found C, 59.23; H, 6.14; N, 20.03; Cl, 12.56.

Example 78**2-(4-Piperidylpyrrolo[4,5-d]pyrimidin-6-yl)thiophene Hydrochloride.**

Using the method described in Example 30 by employing 2-(1-pyrrolidinylvinyl)thiophene (freshly prepared before use) (1.80 g, 10.1 mmol), 4,6-dichloro-5-nitropyrimidine (Aldrich Chemical Company)

160

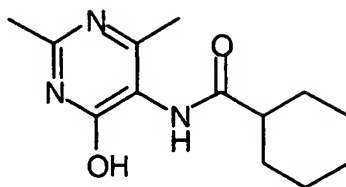
(1.95 g, 10.1 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (1.8 mL, 10.1 mmol), piperidine (2.0 mL, 20.3 mmol), NEt_3 (Aldrich Chemical Company) (2.0 mL) and SnCl_2 (30 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 97:3 CHCl_3 :MeOH as elutant to give 460 mg (16%) of the free base as a beige colored solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.72 (s, 6), 3.83 (s, 4), 6.69 (br s, 1), 7.25 (t, 1, $J =$ 3.9), 7.69 (br s, 1), 7.75 (br s, 1), 8.30 (s, 1), 11.34 (s, 1). MS m/z : 285 ($M+1$). To a solution of 2-(4-Piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)thiophene (0.46 g, 1.63 mmol) in 10:1 EtOAc: MeOH (30 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.63 mL, 1.63 mmol). The precipitate was collected by filtration, washed with EtOAc (2 x 10 mL), ether (3 x 15 mL) and dried under vacuum to give 462 mg (88%) of the title compound as a beige colored solid. Mp: $>280^\circ\text{C}$. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.71 (s, 6), 4.05 (br s, 4), 6.77 (s, 1), 7.26 (t, 1, $J = 4.6$), 7.80 (d, 1, $J = 5.0$), 7.89 (d, 1, $J = 3.6$), 8.59 (s, 1), 12.45 (s, 1), 14.42 (s, 1). MS m/z : 285 ($M+1$ for free base). Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_4\text{S}\cdot\text{HCl}$: C, 56.15; H, 5.34; N, 17.46; Cl, 11.05. Found C, 55.86; H 5.32; N, 17.27; Cl, 11.29.

**Example 79**

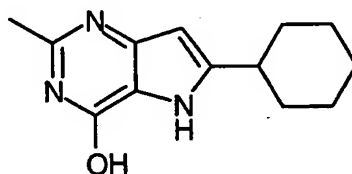
**4-Piperidyl-6-(2-pyridyl)pyrrolo[3,2-*d*]pyrimidine
Hydrochloride Hydrate.**

Using the method described in Example 30 by employing 2-(1-pyrrolidinylvinyl)-2-pyridine (freshly prepared before use) (2.30 g, 13.2 mmol), 4,6-dichloro-5-nitropyrimidine (Aldrich Chemical Company) (2.55 g, 13.2 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (2.3 mL, 13.2 mmol), piperidine (2.1 mL, 21.1 mmol), NEt_3 (Aldrich Chemical Company) (2.0 mL) and SnCl_2 (Aldrich Chemical Company) (40 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl_3 :MeOH as elutant to give 340 mg (9%) of the free base as a beige colored solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.66 (s, 6), 3.76 (s, 4), 7.13 (br s, 1), 7.41 (t, 1, $J = 4.8$), 7.92 (t, 1, $J = 7.4$), 8.10 (d, 1, $J = 8.0$), 8.26 (br s, 1), 8.70 (br s, 1), 11.24 (s, 1). MS m/z : 280 ($M+1$). To a solution of 4-piperidyl-6-(2-pyridyl)pyrrolo[3,2-d]pyrimidine (0.34 g, 1.21 mmol) in 15:1 EtOAc:MeOH (30 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.20 mL, 1.21 mmol). The precipitate was collected by filtration, washed with EtOAc (2 x 10 mL), ether (3 x 15 mL) and dried under vacuum to give 300 mg (79%) of the title compound as a tan colored powder. Mp: 279-280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.72 (s, 6), 4.0 (br s, 4), 7.24 (s, 1), 7.52 (dd, 1, $J = 7.4, 7.5$), 8.01 (dt, 1, $J = 1.3, 7.7$), 8.24 (d, 1, $J = 8.0$), 8.64 (s, 1), 8.77 (d, 1, $J = 4.4$), 12.21 (s, 1), 14.51 (s, 1). MS m/z : 280 ($M+1$). Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_5 \cdot 1.2\text{HCl} \cdot 0.7\text{H}_2\text{O}$: C, 56.91; H, 5.88; N, 20.75; Cl, 13.01. Found C, 56.91; H, 5.83; N, 20.54; Cl, 12.92.

162

**Example 80****(a) 5-Cyclohexyl-2,6-dimethyl-4-hydroxypyrimidine.**

To a slurry of 5-amino-2,6-dimethyl-4-hydroxy
5 pyrimidine hydrochloride (Example 12(a)) (1.36 g, 7.77
mmol) in CH_2Cl_2 (20 mL) was added NEt_3 (Aldrich Chemical
Company) (2.3 mL, 16.3 mmol). The slurry was stirred
at 25 °C under a nitrogen atmosphere for 2-3 min at
which time all material went into solution. To this
10 clear solution was added cyclohexane carbonyl chloride
(Aldrich Chemical Company) (1.4 mL, 10.1 mmol) and
DMAP (Aldrich Chemical Company) (100 mg, catalytic).
This mixture was stirred at 25 °C for 18 h. The
precipitate was collected by filtration, washed with
15 CH_2Cl_2 (3 x 15 mL) and dried under vacuum to provide
1.54 g (80%) of the title compound as a white solid.
 ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.19-1.46 (m, 5), 1.66-
1.84 (m, 5), 2.04 (s, 3), 2.30 (s, 3), 2.39 (br s, 1),
5.80 (s, 1), 8.95 (s, 1). MS m/z : 250 (M+1).

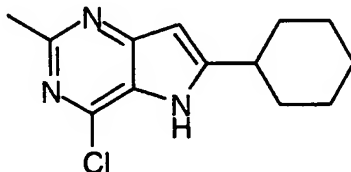


20

(b) 6-Cyclohexyl-2-methylpyrrolo[3,2-d]pyrimidine-4-ol.

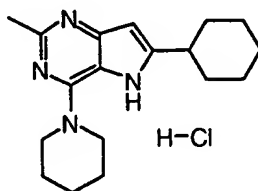
Using the method described in Example 1(d)
(Method B) by employing 5-cyclohexyl-2,6-dimethyl-4-
25 hydroxypyrimidine (Example 80(a)) (1.00 g, 4.02 mmol)
and Na (Aldrich Chemical Company) (0.37 g, 16.1 mmol).
Following the work-up described in Example 1(d) the
residue was purified by flash chromatography on silica

gel with 98:2 CHCl₃:MeOH as elutant to give 355 mg (38%) of the title compound as a beige solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.22-1.44 (m, 5), 1.67 (1, d, *J* = 12.0), 1.76 (d, 2, *J* = 12.5), 1.93 (d, 2, *J* = 11.3),
 5 2.26 (s, 3), 2.60 (tt, 1, *J* = 3.5, 11.3), 5.98 (d, 1, *J* = 2.1), 11.60 (s, 1). MS *m/z* : 232 (M+1).



(c) 4-Chloro-6-cyclohexyl-2-methylpyrrolo[3,2-d]pyrimidine.

10 Using the method described for Example 45(c) by employing 6-cyclohexyl-2-methylpyrrolo[3,2-d]pyrimidine-4-ol (Example 80(b)) (0.33 g, 1.45 mmol) and POCl₃ (Aldrich Chemical Company) (15 mL). Following the work-up described in Example 45(c) the residue was
 15 purified by flash chromatography on silica gel with 98:2 CHCl₃:MeOH as elutant to give 257 mg (71%) of the title compound as a beige solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.37-1.70 (m, 5), 1.86 (d, 1, *J* = 11.8), 1.94 (d, 2, *J* = 12.5), 2.14 (d, 2, *J* = 12.1), 2.73 (s, 3),
 20 2.95 (tt, 1, *J* = 3.5, 11.7), 6.51 (d, 1, *J* = 1.5), 12.19 (s, 1). MS *m/z* : 250 (M+1).

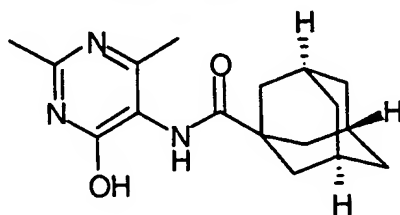


(d) 6-Cyclohexyl-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

25 Using the method described for Example 45(d) by employing 4-chloro-6-cyclohexyl-2-methylpyrrolo[3,2-d]pyrimidine (Example 80(c)) (0.10 g, 0.40 mmol),

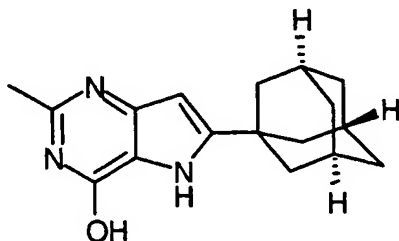
piperidine (Aldrich Chemical Company) (100 mL, 1.00 mmol) and K_2CO_3 (Aldrich Chemical Company) (0.22 g, 1.60 mmol). Flash chromatography of the crude product on silica gel with 95:5 $CHCl_3$:MeOH as elutant gave 144 mg (48%) of the title compound as a beige solid. 1H NMR ($DMSO-d_6$; 400 MHz): δ 1.41 (m, 5), 1.63 (br s, 6), 1.71 (1, d, $J = 13.0$), 1.80 (d, 2, $J = 9.2$), 1.98 (d, 2, $J = 10.4$), 2.37 (s, 3), 2.74 (m, 1), 3.64 (br s, 4), 6.00 (s, 1), 10.62 (s, 1). MS m/z : 299 (M+1). To a solution of 6-cyclohexyl-2-methyl-4-piperidylpyrrolo [3,2-d]pyrimidine (0.13g, 0.46 mmol) in 10:1 EtOAc:MeOH (20 mL : 2 mL) was added 1N HCl in ether (460 mL, 0.46 mmol). After swirling for 5 min the solvent was removed under reduced pressure. The crude material was recrystallized from hot EtOAc to give 121 mg (79%) of the title compound as a beige sandy solid. Mp: $>280^\circ C$. 1H NMR ($DMSO-d_6$; 400 MHz): δ 1.43-1.60 (m, 5), 1.79 (br s, 6), 1.92 (m, 3), 2.10 (br d, 2, $J = 10.9$), 2.65 (s, 3), 3.01 (m, 1), 4.16 (br s, 4), 6.38 (s, 1), 11.90 (s, 1), 14.28 (s, 1). MS m/z : 299 (M+1). Anal. Calcd for $C_{18}H_{26}N_4 \cdot HCl \cdot 0.1H_2O$: C, 64.21; H, 8.14; N, 16.64; Cl, 10.53. Found C, 64.02; H, 8.09; N, 16.55; Cl, 10.87.

25

Example 81**(a) 5-Adamantanyl-2,6-dimethyl-4-hydroxypyrimidine.**

To a slurry of 5-amino-2,6-dimethyl-4-hydroxy pyrimidine hydrochloride (Example 12(a)) (0.94 g, 5.85 mmol) in CH_2Cl_2 (20 mL) was added NEt_3 (Aldrich Chemical Company) (1.7 mL, 12.3 mmol). The slurry was stirred

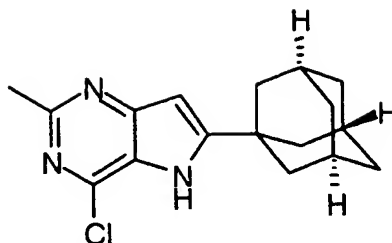
at 25 °C under a nitrogen atmosphere for 2-3 min at which time all material went into solution. To this clear solution was added 1-adamantane carbonyl chloride (Aldrich Chemical Company) (1.5 g, 7.6 mmol) and DMAP (Aldrich Chemical Company) (100 mg, catalytic). This mixture was stirred at 25 °C for 18 h. The precipitate was collected by filtration, washed with CH₂Cl₂ (3 x 15 mL) and dried under vacuum to provide 1.15 g (65%) of the title compound as a white solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.73 (br s, 6), 1.92 (s, 6), 2.01 (s, 3), 2.03 (br s, 1), 2.27 (s, 3), 8.43 (s, 1), 12.47 (s, 1). MS m/z : 302 (M+1).



(b) 6-Adamantan-1-yl-2-methylpyrrolo[3,2-d]pyrimidin-4-ol.

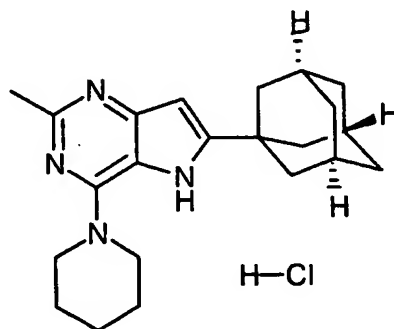
Using the method described in Example 1(d) (Method B) by employing 5-adamantan-1-yl-2,6-dimethyl-4-hydroxypyrimidine (Example 81(a)) (0.82 g, 2.70 mmol) and Na (Aldrich Chemical Company) (0.25 g, 10.8 mmol). Following the work-up described in Example 1(d) the residue was purified by flash chromatography on silica gel with 97:3 CHCl₃:MeOH as elutant to give 120 mg (16%) of the title compound as a beige solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.72 (s, 6), 1.94 (s, 6), 2.02 (s, 3), 2.27 (s, 3), 5.95 (d, 1, J = 2.1), 11.56 (s, 1), 11.62 (s, 1). MS m/z : 284 (M+1).

166



(c) 6-Adamantanylmethyl-4-chloro-2-methylpyrrolo[3,2-d]pyrimidine.

Using the method described for Example 45(c) by
 5 employing 6-adamantanylmethyl-2-methylpyrrolo[3,2-d]
 pyrimidine-4-ol (Example 81(b)) (0.10 g, 0.35 mmol)
 and POCl₃ (Aldrich Chemical Company) (10 mL). Following
 the work-up described in Example 45(c) the residue was
 purified by flash chromatography on silica gel with
 10 98:2 CHCl₃:MeOH as elutant to give 67 mg (61%) of the
 title compound as a brown solid. ¹H NMR (DMSO-d₆; 400
 MHz): δ 1.76 (s, 6), 2.02 (s, 6), 2.08 (s, 3), 2.57 (s,
 3), 6.31 (d, 1, J = 1.8), 11.74 (s, 1). MS m/z : 302
 (M+1).

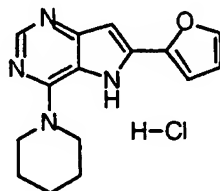


15

(d) 6-Adamantanylmethyl-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

Using the method described for Example 45(d) by
 employing 6-adamantanylmethyl-4-chloro-2-methylpyrrolo[3,2-
 20 d]pyrimidine (Example 81(c)) (65.0 mg, 0.22 mmol),
 piperidine (Aldrich Chemical Company) (110 mL, 1.08
 mmol) and K₂CO₃ (Aldrich Chemical Company) (0.12 g,
 0.90 mmol). Flash chromatography of the crude product

on silica gel with 98:2 CHCl₃:MeOH as elutant gave 41 mg (53%) of the free base as a white solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.63 (s, 6), 1.76 (s, 6), 2.00 (s, 6), 2.06 (s, 3), 2.39 (s, 3), 3.62 (s, 4), 6.04 (s, 1), 10.17 (s, 1). MS m/z : 351 (M+1). To a solution of 6-adamantanyl-2-methyl-4-piperidylpyrrolo [3,2-d]pyrimidine (41.0 mg, 0.12 mmol) in EtOAc (10 mL) was added 1N HCl in ether (120 mL, 0.12 mmol). After swirling for 5 min the solvent was removed under reduced pressure to give 34 mg (74%) of the title compound as a beige solid. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.49 (br s, 6), 1.60 (s, 6), 1.85 (s, 6), 1.90 (s, 3), 2.32 (s, 3), 3.80 (s, 4), 6.06 (s, 1), 10.83 (s, 1), 13.87 (s, 1). MS m/z : 351 (M+1). Anal. Calcd. for C₂₂H₃₀N₄•HCl•1.0H₂O: C, 65.24; H, 8.21; N, 13.84; Cl, 8.75. Found C, 65.06; H, 7.76; N, 13.69; Cl, 8.82.



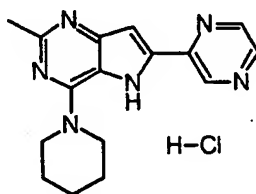
20

Example 82**2-(4-Piperidylpyrrolo[4,5-d]pyrimidin-6-yl)furan Hydrochloride.**

Using the method described in Example 30 by employing 2-(1-pyrrolidinylvinyl)furan (freshly prepared before use) (2.13 g, 13.1 mmol), 4,6-dichloro-5-nitropyrimidine (Aldrich Chemical Company) (2.51 g, 13.1 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (2.2 mL, 13.1 mmol), piperidine (Aldrich Chemical Company) (2.1 mL, 21.0 mmol), NEt₃ (Aldrich Chemical Company) (2.0 mL) and SnCl₄ (49 mL of a 2M solution in DMF). The residue was

purified by flash chromatography on silica gel with 95:5 CHCl₃:MeOH as elutant to give 162 mg (5%) of the free base as a tan colored sandy solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.65 (br s, 6), 3.72 (br s, 4), 6.67 (br s, 2), 7.12 (s, 1), 7.83 (s, 1), 8.23 (s, 1), 11.27 (s, 1). MS m/z : 269 (M+1). To a solution of 2-(4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)furan (0.54 g, 1.81 mmol) in 5:1 EtOAc: MeOH (30 mL) was added 1M ethereal HCl (Aldrich Chemical Company) (1.80 mL, 1.80 mmol). The precipitate was collected by filtration, washed with EtOAc (2 x 10 mL), ether (3 x 15 mL) and dried under vacuum to give 550 mg (92%) of the title compound as a beige colored solid. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.71 (s, 6), 4.04 (br s, 4), 6.75 (dd, 1, J = 3.1, 3.3), 6.83 (s, 1), 7.39 (s, 1), 7.96 (s, 1), 8.60 (s, 1), 12.27 (s, 1), 14.32 (s, 1). MS m/z : 269 (M+1). Anal. Calcd for C₁₅H₁₆N₄O·HCl: C, 59.11; H, 5.62; N, 18.38; Cl, 11.63. Found C, 58.84; H, 5.72; N, 18.16; Cl, 11.54.

20

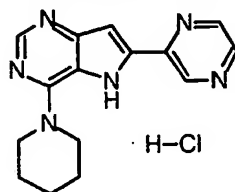
Example 83**2-Methyl-4-piperidyl-6-pyrazin-2-ylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

25 Using the method described in Example 30 by employing 2-(1-pyrrolidinylvinyl)pyrazine (freshly prepared before use) (2.15 g, 12.3 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.50 g, 12.3 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (2.1 mL, 12.3 mmol), piperidine (Aldrich Chemical Company) (1.9 mL, 19.7 mmol), NEt₃,

30

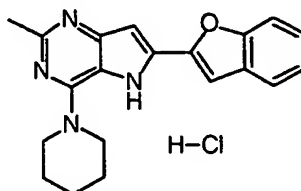
(Aldrich Chemical Company) (2.0 mL) and SnCl_2 (37 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl_3 :MeOH as elutant to give 116 mg (4%) of the free base as a brown colored solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.66 (br s, 6), 2.44 (s, 3), 3.30 (s, 2, under H_2O), 3.77 (br s, 2), 6.80-7.15 (m, 1), 8.91 (br s, 2), 9.33 (s, 1), 11.42 (s, 1). MS m/z : 295 ($M+1$). To a hot solution of 2-methyl-4-piperidyl-6-pyrazin-2-ylpyrrolo [3,2-d]pyrimidine (0.12 g, 0.39 mmol) in 10:1 EtOAc:MeOH (30 mL) was added 1N etheral HCl (Aldrich Chemical Company) (0.40 mL, 0.39 mmol). Crystallization occurred as the mixture cooled and the precipitate was collected by filtration, washed with Et_2O (3 x 10 mL), and dried under vacuum to give 68 mg (53%) of the title compound as a brown colored solid. Mp: 280-283.5 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.72 (s, 6), 2.59 (s, 3), 4.08 (br s, 4), 7.29 (s, 1), 8.74 (d, 1, $J = 2.4$), 8.82 (br s, 1), 9.49 (s, 1), 12.41 (s, 1), 14.41 (s, 1). MS m/z : 295 ($M+1$ for free base). Anal. Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_6 \cdot \text{HCl} \cdot 1.4\text{H}_2\text{O}$: C, 54.07; H, 5.64; N, 23.65; Cl, 10.19. Found C, 54.32; H, 5.69; N, 23.26; Cl, 10.18.

25

Example 84**4-Piperidyl-6-pyrazin-2-ylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

Using the method described in Example 30 by employing 2-(1-pyrrolidinylnyl)pyrazine (freshly prepared before use) (2.39 g, 13.7 mmol), 4,6-

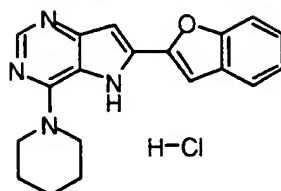
dichloro-5-nitropyrimidine (Aldrich Chemical Company) (2.60 g, 13.7 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (2.4 mL, 13.7 mmol), piperidine (Aldrich Chemical Company) (2.2 mL, 21.9 mmol), NET_3 (Aldrich Chemical Company) (2.0 mL) and SnCl_2 (41 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl_3 :MeOH as elutant to give 143 mg (4%) of the free base as a beige colored solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.67 (br s, 6), 3.77 (s, 4), 7.28 (s, 1), 8.28 (s, 1), 8.63 (s, 1), 8.74 (s, 1), 9.36 (s, 1), 11.48 (s, 1). MS m/z : 281 (M+1). To a hot solution of 4-piperidyl-6-pyrazin-2-ylpyrrolo[3,2-d]pyrimidine (0.14 g, 0.51 mmol) in 10:1 EtOAc: MeOH (40 mL) was added 1M ethereal HCl (Aldrich Chemical Company) (0.51 mL, 0.51 mmol). Crystallization occurred as the mixture cooled and the precipitate was collected by filtration. The crystals were washed with Et_2O (3 x 10 mL) and dried under vacuum to give 128 mg (80%) of the title compound as a beige colored solid. Mp: $>280^\circ\text{C}$. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.73 (s, 6), 4.10 (s, 4), 7.37 (s, 1), 8.66 (s, 1), 8.75 (d, 1, $J = 2.5$), 8.83 (t, 1, $J = 1.5$), 9.49 (d, 1, $J = 1.2$), 12.53 (s, 1), 14.56 (s, 1). MS m/z : 281 (M+1). Anal. Calcd for $\text{C}_{15}\text{H}_{16}\text{N}_6 \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$: C, 56.00; H, 5.49; N, 26.13; Cl, 11.10. Found C, 56.00; H, 5.49; N, 26.11; Cl, 11.09.

Example 85

2-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzo[b]furan Hydrochloride Monohydrate.

Using the method described in Example 30 by employing 2-(1-pyrrolidinylvinyl)benzo[b]furan (freshly prepared before use) (2.21 g, 10.4 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.10 g, 10.4 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (1.8 mL, 10.4 mmol), piperidine (Aldrich Chemical Company) (1.6 mL, 16.6 mmol), NEt_3 (Aldrich Chemical Company) (2.0 mL) and SnCl_2 (31 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl_3 :MeOH as elutant to give 560 mg (16%) of the free base as a beige colored solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.67 (s, 6), 2.44 (s, 3), 3.30 (s, 2, under H_2O), 3.74 (s, 2), 6.83 (m, 1), 7.28 (br s, 3), 8.77 (br s, 2), 11.36 (s, 1). MS m/z : 333 ($M+1$). To a hot solution of 2-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzo[b]furan (Example 85(a)) (0.56 g, 1.69 mmol) in 5:1 EtOAc: MeOH (30 mL) was added 1M ethereal HCl (Aldrich Chemical Company) (1.70 mL, 1.69 mmol). Upon cooling crystallization occurred and the solid was collected by filtration. This material was washed with Et_2O (2 x 10 mL) and dried under vacuum to give 588 mg (95%) of the title compound as a beige colored solid. Mp: $>280^\circ\text{C}$. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.73 (s, 6), 2.58 (s, 3), 4.08 (s, 4), 7.00 (s, 1), 7.35 (t, 1, $J = 7.5$), 7.44 (t, 1, $J = 8.0$), 7.71 (d, 1, $J = 8.2$), 7.79 (d, 1, $J = 7.7$), 7.88 (s, 1), 12.48 (s, 1), 14.40 (s, 1). MS m/z : 333 ($M+1$). Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}\cdot\text{HCl}\cdot\text{H}_2\text{O}$: C, 62.25; H, 5.71; N, 14.52; Cl, 9.19. Found C, 62.22; H, 5.94; N, 14.54; Cl, 9.22.

Example 86

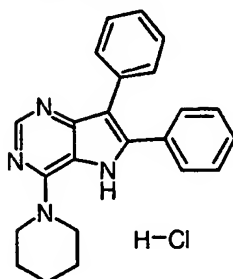


**2-(4-Piperidylpyrrolo[4,5-d]pyrimidin-6-yl)
benzo[b]furan Hydrochloride Hydrate.**

- 5 Using the method described in Example 30 by
employing 2-(1-pyrrolidinylvinyl) benzo[b]furan
(freshly prepared before use) (2.29 g, 10.7 mmol),
4,6-dichloro-5-nitropyrimidine (Aldrich Chemical
Company) (2.10 g, 10.7 mmol), *N,N*-diisopropylethyl
10 amine (Aldrich Chemical Company) (1.9 mL, 10.7 mmol),
piperidine (Aldrich Chemical Company) (1.7 mL, 17.1
mmol), NEt_3 (Aldrich Chemical Company) (2.0 mL) and
 SnCl_2 (32 mL of a 2M solution in DMF). The residue was
purified by flash chromatography on silica gel with
15 95:5 CHCl_3 :MeOH as elutant to give 612 mg (18%) of the
free base as a tan colored solid. ^1H NMR ($\text{DMSO}-d_6$; 400
MHz): δ 1.68 (s, 6), 3.77 (s, 4), 6.94 (s, 1), 7.32
(d, 2, $J = 18.9$), 7.68 (t, 3, $J = 26.3$), 8.28 (s, 1),
11.54 (s, 1). MS m/z : 319 (M+1). To a hot solution
20 of 2-(4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzo[b]
furan (0.61 g, 1.92 mmol) in 3:1 EtOAc: MeOH (50 mL)
was added 1M ethereal HCl (Aldrich Chemical Company)
(1.90 mL, 1.92 mmol). Upon cooling crystallization
occurred and the solid was collected by filtration.
25 This material was washed with Et_2O (2 x 10 mL) and
dried under vacuum to give 612 mg (90%) of the title
compound as a brown colored solid. Mp: 278.5-281 °C.
 ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.74 (s, 6), 4.10 (s, 4),
7.09 (s, 1), 7.36 (t, 1, $J = 7.5$), 7.45 (t, 1, $J =$
30 7.9), 7.72 (d, 1, $J = 8.3$), 7.80 (d, 1, $J = 7.7$), 7.93
(s, 1), 8.64 (s, 1), 12.76 (s, 1), 14.66 (s, 1). MS

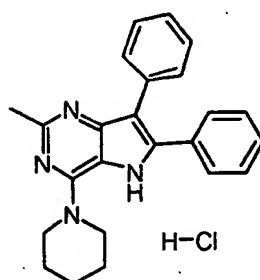
m/z : 319 (M+1). Anal. Calcd for $C_{19}H_{18}N_4O \cdot HCl \cdot 0.5H_2O$:
C, 62.80; H, 5.41; N, 15.42; Cl, 9.76. Found C,
62.89; H, 5.46; N, 15.36; Cl, 9.89.

5

Example 87**6,7-Diphenyl-4-piperidylpyrrolo[3,2-d]pyrimidine
Hydrochloride Hydrate.**

Using the method described in Example 30 by
10 employing (1,2-diphenylvinyl)pyrrolidine (freshly
prepared before use) (1.85 g, 7.43 mmol), 4,6-
dichloro-5-nitropyrimidine (Aldrich Chemical Company)
(1.40 g, 7.43 mmol), *N,N*-diisopropylethyl amine
(Aldrich Chemical Company) (1.3 mL, 7.43 mmol),
15 piperidine (1.2 mL, 11.9 mmol), NEt₃ (Aldrich Chemical
Company) (2.0 mL) and SnCl₄ (Aldrich Chemical Company)
(22 mL of a 2M solution in DMF). The residue was
purified by flash chromatography on silica gel with
95:5 CHCl₃:MeOH as elutant to give 258 mg (10%) of the
20 free base as a brown colored sandy solid. ¹H NMR
(DMSO-*d*₆; 400 MHz): δ 1.66 (br s, 6), 3.75 (br s, 4),
7.19 (t, 1, J = 7.3), 7.29 (t, 2, J = 7.7), 7.42-7.47
(m, 7), 8.30 (s, 1), 11.38 (s, 1). MS m/z : 355 (M+1).
To a solution of 6,7-diphenyl-4-piperidylpyrrolo[3,2-
25 d]pyrimidine (0.26 g, 0.73 mmol) in 4:1 EtOAc: MeOH
(30 mL) was added 1M ethereal HCl (Aldrich Chemical
Company) (730 mL, 0.73 mmol). The precipitate was
collected by filtration, washed with ether (3 x 15 mL)
and dried under vacuum to give 258 mg (91%) of the

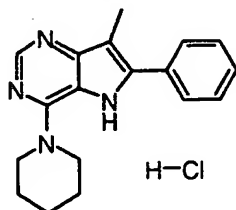
title compound as a beige colored solid. Mp: 266-268.5 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.73 (br s, 6), 4.09 (br s, 4), 7.29 (d, 2, J = 6.7), 7.37-7.44 (m, 8), 8.50 (s, 1), 12.42 (s, 1), 14.15 (s, 1). MS m/z : 355 (M+1). Anal. Calcd for C₂₃H₂₂N₄•HCl•0.25H₂O: C, 69.92; H, 5.99; N, 14.18; Cl, 8.97. Found C, 69.92; H, 6.01; N, 13.86; Cl, 9.37.

Example 88**2-Methyl-6,7-diphenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

Using the method described in Example 30 by employing (1,2-diphenylvinyl)pyrrolidine (freshly prepared before use) (1.83 g, 7.35 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.50 g, 7.35 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (1.3 mL, 7.35 mmol), piperidine (1.2 mL, 11.8 mmol), NEt₃ (Aldrich Chemical Company) (2.0 mL) and SnCl₄ (Aldrich Chemical Company) (22 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃:MeOH as elutant to give 110 mg (4%) of the free base as a pale yellow colored solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.65 (br s, 6), 2.42 (s, 3), 3.72 (br s, 4), 7.19 (m, 1), 7.28 (m, 2), 7.39-7.44 (m, 7), 11.20 (s, 1). MS m/z : 369 (M+1). To a solution of 2-methyl-6,7-diphenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (148 g, 0.40 mmol) in 1:1 EtOAc: MeOH (50 mL) was added 1M ethereal HCl

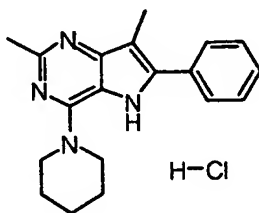
175

(Aldrich Chemical Company) (400 mL, 0.40 mmol). The solvent was removed under reduced pressure and then dried under vacuum to give 83 mg (51%) of the title compound as a beige colored solid. Mp: 169-171 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.72 (br s, 6), 2.56 (s, 3), 4.06 (br s, 4), 7.29 (dd, 2, J = 1.7, 6.0), 7.37-7.45 (m, 8), 12.26 (s, 1), 13.40 (s, 1). MS m/z : 369 (M+1). Anal. Calcd. for C₂₄H₂₄N₄•HCl•H₂O: C, 68.25; H, 6.40; N, 13.27; Cl, 8.29. Found C, 68.33; H, 6.41; N, 13.15; Cl, 8.50.

Example 89**7-Methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.**

Using the method described in Example 30 by employing (1-phenylbut-1-enyl)pyrrolidine (freshly prepared before use) (2.10 g, 11.3 mmol), 4,6-dichloro-5-nitropyrimidine (Aldrich Chemical Company) (2.18 g, 11.3 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (2.0 mL, 11.3 mmol), piperidine (1.8 mL, 18.1 mmol), NEt₃ (Aldrich Chemical Company) (2.0 mL) and SnCl₄ (Aldrich Chemical Company) (34 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃:MeOH as elutant to give 407 mg (12%) of the product as a faint yellow colored solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.64 (br s, 6), 2.30 (s, 3), 3.72 (br s, 4), 7.44 (t, 1, J = 7.3), 7.53 (t, 2, J = 7.53), 7.66 (d, 2, J = 7.3), 8.29 (s, 1), 10.95 (s, 1). MS m/z : 293 (M+1). To a solution of 7-methyl-6-phenyl-

4-piperidylpyrrolo[3,2-d]pyrimidine (0.22 g, 0.76 mmol) in 5:1 EtOAc: MeOH (30 mL) was added 1M ethereal HCl (Aldrich Chemical Company) (760 mL, 0.73 mmol). The precipitate was collected by filtration, washed with ether (3 x 15 mL) and dried under vacuum to give 224 mg (90%) of the title compound as a white colored solid. Mp: 281-282.5 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.71 (br s, 6), 2.32 (s, 3), 4.04 (br s, 4), 7.52-7.61 (m, 3), 7.68 (d, 2, *J* = 7.1), 8.56 (s, 1), 12.05 (s, 1), 14.67 (s, 1). MS *m/z*: 293 (M+1). Anal. Calcd. for C₂₄H₂₄N₄•HCl: C, 65.74; H, 6.44; N, 17.04; Cl, 10.78. Found C, 65.64; H, 6.51; N, 17.04; Cl, 10.71.



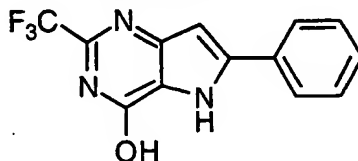
15

Example 90**2,7-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.**

Using the method described in Example 30 by employing (1-phenylbut-1-enyl)pyrrolidine (freshly prepared before use) (2.13 g, 11.5 mmol), 4,6-dichloro-5-nitropyrimidine (Aldrich Chemical Company) (2.30 g, 11.5 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (2.0 mL, 11.5 mmol), piperidine (1.8 mL, 18.4 mmol), NEt₃ (Aldrich Chemical Company) (2.0 mL) and SnCl₂ (Aldrich Chemical Company) (35 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃:MeOH as elutant to give 304 mg (9%) of the free base as a beige colored fluffy solid. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.63 (br s, 6), 2.27 (s, 3), 2.44 (s, 3), 3.71 (br s, 4), 7.43 (t, 1, *J* = 7.3), 7.52 (t,

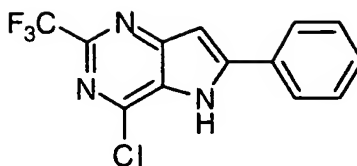
2, $J = 7.6$), 7.65 (d, 2, $J = 7.4$), 10.79 (s, 1). MS m/z : 307 (M+1). To a solution of 2,7-dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (0.22 g, 0.76 mmol) in 5:1 EtOAc: MeOH (30 mL) was added 1M
5 etheral HCl (Aldrich Chemical Company) (760 mL, 0.73 mmol). The precipitate was collected by filtration, washed with ether (3 x 15 mL) and dried under vacuum to give 224 mg (90%) of the title compound as a white colored solid. Mp: $>280^{\circ}\text{C}$. ^1H NMR (DMSO- d_6 ; 400 MHz):
10 δ 1.69 (br s, 6), 2.35 (s, 3), 2.64 (s, 3), 4.03 (br s, 4), 7.52-7.60 (m, 3), 7.65-7.68 (m, 2), 11.94 (s, 1), 14.16 (s, 1). MS m/z : 307 (M+1). Anal. Calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_4 \cdot 1.1\text{HCl} \cdot \text{H}_2\text{O}$: C, 62.74; H, 6.95; N, 15.41; Cl, 10.50. Found C, 63.09; H, 7.00; N, 15.39; Cl, 10.54.

15

Example 91**(a) 6-Phenyl-2-(trifluoromethyl)pyrrolo[3,2-d]pyrimidine-4-ol.**

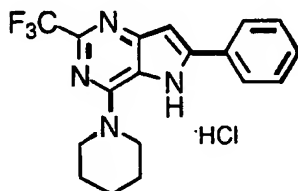
20 The mixture of ethyl 3-amino-5-phenylpyrrole-2-carboxylate (Example 66(b)) (2.3 g, 10 mmol) and trifluoromethylacetamide (Aldrich Chemical Company) (1.457 g, 13 mmol) in 20 mL of o-xylene was heated under reflux for 15 h. The solvent was evaporated
25 under reduced pressure to give a dark-red residue, and toluene was added. The precipitate that formed was collected by filtration, and dried in a vacuum oven overnight to give 1.847 g (66%) of the title compound as a tan solid. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 7.06 (s,
30 1), 7.38-7.49 (m, 3), 7.98 (d, 2, $J = 7.39$), 12.74 (br s, 1); MS m/z : 280 (M+1), 278 (M-1).

178



(b) 4-Chloro-6-phenyl-2-(trifluoromethyl)pyrrolo[3,2-d]pyrimidine.

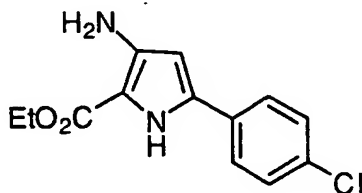
A mixture of 6-phenyl-2-(trifluoromethyl)pyrrolo
5 [3,2-d]pyrimidine-4-ol (Example 91(a)) (1.847 g, 6.62
mmol) and phosphoryl oxychloride (Aldrich Chemical
Company) (15 mL, 166 mmol) was heated at 120 °C for 36
h. POCl₃ was removed under reduced pressure, and to
the residue was added ice-water followed by ammonia
10 water to pH 8. The resulting mixture was extracted
three times with EtOAc. The combined organic layers
were washed with brine, dried over Na₂SO₄, concentrated
in vacuo, and dried in a vacuum oven overnight to
give 1.249 g (63%) of the title compound as a brown
15 solid. ¹H NMR (CDCl₃; 500 MHz): δ 7.13 (s, 1), 7.51-
7.58 (m, 3), 7.79 (d, 2, J = 7.48), 9.15 (br s, 1).
MS m/z: 298, 300 (M+1); 296, 298 (M-1).



**(c) 6-Phenyl-4-piperidyl-2-(trifluoromethyl)pyrrolo
20 [3,2-d]pyrimidine Hydrochloride Monohydrate.**

To a 25-mL, round-bottomed flask were added 4-
chloro-6-phenyl-2-(trifluoromethyl)pyrrolo[3,2-d]
pyrimidine (Example 91(b)) (0.4 g, 1.34 mmol) and
piperidine (Aldrich Chemical Company) (0.66 mL, 6.72
25 mmol), followed by addition of a solution of potassium
carbonate (1.85 g, 13.4 mmol) in 8 mL of water. The
reaction mixture was stirred at 120 °C for 15 h. After
cooling to room temperature, the precipitate formed

was collected by filtration, washed with water and hexane to give a tan solid. The material was purified by flash chromatography on silica gel with 1:4 of EtOAc:hexane as eluent to give 0.361 g (78%) of a light-pink solid. This material (355 mg, 1.03 mmol) was dissolved in minimum amount of CHCl_3 , and ethereal hydrogen chloride (1N, 1.1 mL, 1.1 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min. Solvent was then evaporated *in vacuo* to give a foam, which was recrystallized from MeOH/ H_2O to give 104 mg of the title compound as light-pink crystals. Mp: 235.1- 237.5 °C (dec). ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.68 (m, 6), 3.84-3.85 (m, 4), 7.02 (s, 1), 7.44-7.55 (m, 3), 7.93 (d, 2, $J = 7.68$), 11.53 (br s, 1). MS m/z : 347 ($M+1$), 345 ($M-1$). Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{ClF}_3\text{N}_4 \cdot \text{H}_2\text{O}$: C, 53.94; H, 5.03; N, 13.98; Cl, 8.84. Found: C, 54.03; H, 5.02; N, 13.83, Cl, 8.98.

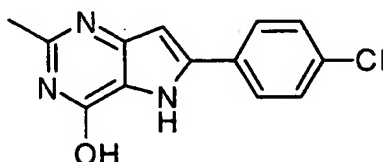


Example 92

(a) Ethyl 3-amino-5-(4-chlorophenyl)pyrrole-2-carboxylate.

Sodium ethoxide was prepared freshly from Na (2.09 g, 91 mmol) and EtOH (25 mL). To this solution was added a solution of 3-chloro-3-(4-chlorophenyl)acrylonitrile (Maybridge Chemical Company) (6.00 g, 30.3 mmol), and aminodiethyl malonate hydrochloride (Aldrich Chemical Company) (6.41 g, 30.3 mmol) in EtOH (55 mL) through a dropping funnel. After the addition was completed, the reaction mixture was stirred at room temperature for 21 h. The solvent was evaporated *in vacuo* and the

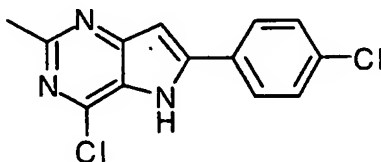
residue was partitioned between EtOAc and H₂O. The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo to give 4.266 g of a dark-red solid. It was used in the following step without purification.



(b) 6-(4-Chlorophenyl)-2-methylpyrrolo[3,2-d]pyrimidin-4-ol.

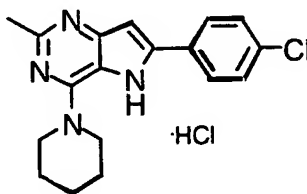
Dry HCl gas was bubbled through a solution of ethyl 3-amino-5-(4-chlorophenyl)pyrrole-2-carboxylate (Example 92(a)) (3.78 g) in 90 mL of acetonitrile at room temperature for 1.5 h. The reaction mixture was then capped, and stirred at room temperature overnight. The solvent was evaporated in vacuo to give a brown residue, which was dissolved in 50 mL of EtOH and 25 mL of 6% aqueous sodium hydroxide. The reaction mixture was heated at reflux for 6 h. The precipitate formed was filtered, and dried in a vacuum oven to give 0.657 g of the title compound as a brown solid. The filtrate was concentrated down and the resulting viscous solid was separated. Toluene was added and the solution evaporated in vacuo. CH₂Cl₂ was added to the residue. The precipitate formed was filtered, washed with water, and dried in a vacuum oven to give 0.693 g (total yield 19%) of the title compound as a tan solid.

¹H NMR (DMSO-d₆; 500 MHz) δ 2.31 (s, 3), 6.79 (s, 1), 7.49 (d, 2, J = 8.42), 7.95 (d, 2, J = 8.58), 11.79 (br s, 1), 12.32 (br s, 1).



(c) 4-Chloro-6-(4-chlorophenyl)-2-methylpyrrolo[3,2-d]pyrimidine.

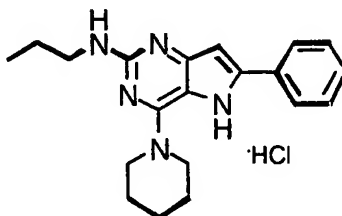
A mixture of 6-(4-chlorophenyl)-2-methylpyrrolo
[3,2-d]pyrimidin-4-ol (Example 92(b)) (1.35 g, 5.2
5 mmol) and phosphorus oxychloride (Aldrich Chemical
Company) (12 mL, 130 mmol) was heated at 120 °C for 24
h. The excess POCl₃ was removed under reduced pressure
to give a dark-brown residue. The residue was diluted
with ice-water and neutralized under stirring and
10 cooling with ammonia water to pH 8. The resulting
mixture was extracted three times with EtOAc. The
combined organic layers were washed with brine, dried
over Na₂SO₄ and concentrated in vacuo to give 0.654 g
(45%) of the title compound as a brown solid. ¹H NMR
15 (DMSO-d₆; 500 MHz): δ 2.78 (s, 3), 6.90 (s, 1), 7.49
(d, 2, J = 7.5), 7.69 (d, 2, J = 7.22), 8.91 (br s,
1); MS m/z: 278, 280 (M+1); 276, 278 (M-1).



(d) 6-(4-Chlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.

To a 25-mL, round-bottomed flask were added 4-
chloro-6-(4-chlorophenyl)-2-methylpyrrolo[3,2-d]
pyrimidine (Example 92(c)) (0.3 g, 1.08 mmol) and
piperidine (Aldrich Chemical Company) (0.53 mL, 5.4
25 mmol), followed by addition of a solution of potassium
carbonate (1.49 g, 10.8 mmol) in 10 mL of water. The
reaction mixture was stirred at 120 °C for 4 h. After
cooling to room temperature, the precipitate that
formed was collected by filtration, washed with water
and hexane, and dried in a vacuum oven to give 0.355 g
30 of a brown solid. This material (346 mg, 1.06 mmol)

was dissolved in minimum amount of CHCl_3 , ethereal hydrogen chloride (1N, 1.1 mL, 1.1 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min. The solvent was then evaporated in vacuo to give a foam, which was recrystallized from MeOH/ H_2O to give 138 mg of the title compound as tan crystals. Mp: 253.8- 255.2 (dec). ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.70-1.71 (m, 6), 2.57 (s, 3), 4.06-4.07 (m, 4), 6.94 (s, 1), 7.63 (d, 2, $J = 8.60$), 8.01 (d, 2, $J = 8.6$), 12.0 (br s, 1), 14.3 (br s, 1); MS m/z : 327, 329 (M+1), 325, 327 (M-1). Calcd for $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{N}_4 \cdot \text{H}_2\text{O}$: C, 56.70; H, 5.82; N, 14.69; Cl, 18.60. Found: C, 56.45; H, 5.79; N, 14.60, Cl, 18.42.



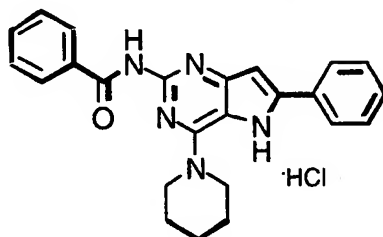
15

Example 93**(6-Phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-yl)propylamine Hydrochloride.**

To a solution of 6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-ylamine (Example 66(e)) (100 mg, 0.34 mmol) in MeOH (3.5 mL) in a 25-mL round-bottomed flask were added propionaldehyde (0.074 mL, 1.02 mmol) and sodium cyanoborohydride (Aldrich Chemical Company) (43 mg, 0.68 mmol). The pH of the reaction was adjusted to 6 by the addition of methanolic hydrogen chloride. The reaction was heated at reflux for 40 h. The pH was lowered to 4 by addition of 10% HCl and the reaction was stirred for 1 h. The pH was raised to 10 by addition of saturated Na_2CO_3 . The solvent was removed in vacuo and the residue was dissolved in water and extracted with CH_2Cl_2 three times. The

combined organic layers were dried over Na_2SO_4 , concentrated in vacuo to give an orange oil. The residue was purified by preparative TLC using 95:5 CHCl_3 :MeOH as eluent to give 32 mg (28%) of a light-yellow solid. The above material was dissolved in CHCl_3 (2 mL). Ethereal hydrogen chloride (1N, 0.25 mL, 0.25 mmol) was added. The mixture was stirred at room temperature for 20 min. Solvent was evaporated to give 33 mg of the title compound as a light-yellow solid. ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 0.93 (t, 3, J = 7.22), 1.58-1.62 (m, 2), 1.68 (m, 6), 3.25 (m, 2), 3.96 (m, 4), 6.66 (s, 1), 7.45-7.54 (m, 3), 7.68 (br s, 1), 7.86 (d, 2, J = 7.32), 11.54 (br s, 1), 12.23 (br s, 1). MS m/z : 336 ($M+1$), 334 ($M-1$). Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_5 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 63.06; H, 7.14; N, 18.39. Found: C, 63.06; H, 6.93; N, 18.29.

Example 94

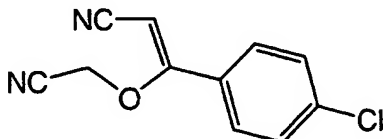


20 Phenyl-N-(6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-yl)formamide Hydrochloride Hydrate.

To a mixture of 6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-ylamine (Example (66(e))) (100 mg, 0.34 mmol) in pyridine (7 mL) in a 25-mL, round-bottomed flask was added benzoic anhydride (81 mg, 0.36 mmol). The reaction was heated at reflux for 15 h. The solvent was removed in vacuo and 0.1 M NaOH (10 mL) was added to the residue. The precipitate that formed was filtered, washed with water, dried in a vacuum oven overnight to give 156 mg of an orange solid. The

184

above material was dissolved in CHCl_3 (10 mL).
Ethereal hydrogen chloride (1N, 0.35 mL, 0.35 mmol)
was added. The mixture was stirred at room
temperature for 20 min. The solvent was evaporated to
5 give a foam, which was recrystallized from MeOH/H₂O to
give 30 mg of the title compound as orange crystals.
¹H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.74 (m, 6), 4.09 (m, 4),
7.07 (s, 1), 7.50-7.74 (m, 6), 7.89 (d, 2, $J = 7.63$),
8.08 (d, 2, $J = 7.67$), 11.85 (br s, 1), 11.94 (br s,
10 1), 13.61 (br s, 1). MS m/z : 398 (M+1), 396 (M-1).
Anal. Calcd for $\text{C}_{24}\text{H}_{24}\text{ClN}_4\text{O} \cdot 2.2\text{H}_2\text{O}$: C, 60.88; H, 6.04; N,
14.80; Cl, 7.49. Found: C, 60.88; H, 5.77; N, 14.63,
Cl, 7.38.

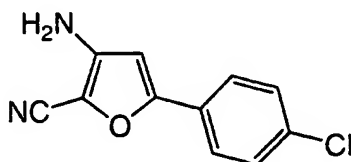


15

Example 95**(a) 3-(4-Chlorophenyl)-3-(cyanomethoxy)-prop-2-ene nitrile.**

Glycolonitrile (Aldrich Chemical Company) (5.0g,
20 43.8 mmol, 55 wt.% in H₂O) was dissolved in THF (20
mL) and MgSO_4 was added. The mixture was stirred for
10 min and filtered into a 250-mL round-bottomed
flask. The solution was cooled to 0 °C and NaH
(Aldrich Chemical Company) (1.75 g, 43.8 mmol, 60%)
25 was added in portions over 15 min with stirring.
After this addition, the mixture was stirred for
another 30 min at 0 °C and 30 min at room temperature.
A solution of 4-chlorophenyl-acrylonitrile (4.34 g,
21.9 mmol, Maybridge) in THF (10 ml) was added
30 dropwise over 5 min. The resulting solution was
stirred at RT overnight. The reaction was poured onto
ice (100 g) and extracted with Et₂O (3x100mL). The

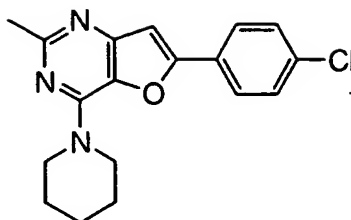
combined organic layers were washed with brine (200 mL) and dried over MgSO₄, filtered, and evaporated to give a crude oil. Chromatography on flash silica gel (100% Hexanes to 20% EtOAc/Hexanes) gave 750 mg (15.7%) of a yellow solid. Mp: 87-88 °C. ¹H NMR (CDCl₃, 400 MHz): δ 5.06 (s, 2), 5.23 (s, 2), 7.44-7.50 (m, 4).



(b) 3-Amino-5-(4-chlorophenyl)-furan-2-carbonitrile.

10 The dinitrile (Example 95(a)) (500 mg, 2.29 mmol) was dissolved in THF (10 mL) and cooled to -78 °C with stirring under nitrogen. To this mixture was added a solution of NaOCH₃ (Aldrich Chemical Company) (0.53 mL, 2.30 mmol, 25 wt.%) dropwise over a 2 min. The
15 reaction was stirred at -78 °C for 1 h, then allowed to warm to room temperature. At room temperature, the mixture was poured onto ice (50 g) and extracted with Et₂O (3x100 mL). The combined organic layers were washed with brine (200 mL) and dried over MgSO₄,
20 filtered, and evaporated to give a crude oil. Chromatography on flash silica gel (33% EtOAc/Hexanes) gave 444 mg (89%) of a yellow solid. Mp: 147-148° C. ¹H NMR (CDCl₃, 400 MHz): δ 3.91 (s, 2), 6.34 (s, 1), 7.38 (d, 2, J = 8.5), 7.58 (d, 2, J = 8.5). The side
25 product isolated in 10% yield resulted from the hydrolysis of the nitrile to give the methyl ester.

186

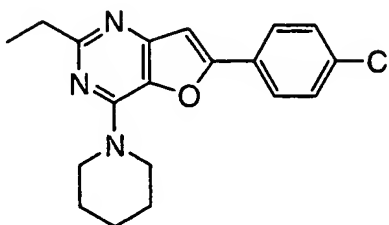


(c) 6-(4-Chlorophenyl)-2-methyl-4-piperidinylfurano-[3,2-d]-pyrimidine Hydrochloride Hydrate.

N,N-dimethylacetamide (Aldrich Chemical Company) (88 μ L, 0.95 mmol) was added dropwise to POCl₃ (Aldrich Chemical Company) (10 mL) and stirred at room temperature under nitrogen for 1 h. To this solution was added the aminonitrile furan (Example 95(b)) (200 mg, 0.915 mmol), and the resulting solution was heated at reflux for 16 h. The reaction was allowed to cool to room temperature and the solvent was evaporated in vacuo to leave a residue. The residue was dissolved in piperidine (10 mL) and the mixture was heated at reflux for 16 h. The reaction was cooled to room temperature and taken up in EtOAc (150 mL). The organic layer was washed with saturated NaHCO₃ (3x100 mL), brine (100 mL) and dried over MgSO₄, filtered and evaporated at reduced pressure to give an oil. Chromatography on silica gel (50 % EtOAc/Hexanes) gave 193 mg (64 %) of a yellow solid. The furanyl pyrimidine (150 mg, 0.457 mmol) was dissolved in EtOAc (10 mL) and stirred rapidly as ethereal HCl (0.46 mL, 0.46 mmol, 1.0 M) was added dropwise. The mixture immediately became cloudy. After 1 h, the product was filtered and dried in a vacuum oven at 60 °C to give 160 mg (97 % yield). Mp: > 288° C. ¹H NMR (CDCl₃, 400 MHz): δ 1.75 (br s, 6), 2.59 (s, 3), 4.16 (br s, 4), 7.67 (br d, 3, *J* = 6.4), 8.11 (br d, 2, *J* = 7.1). MS *m/z* 328 (M+1). Anal Calcd for C₁₈H₁₈ClN₃O.

HCl•0.75H₂O: C, 57.24; H, 5.47; N, 11.13; Cl, 18.77.

Found: C, 57.24; H, 5.41; N, 11.16; Cl, 18.65.

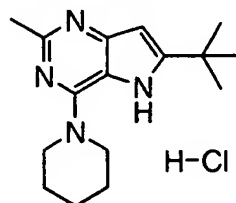


5

Example 96**6-(4-Chlorophenyl)-2-ethyl-4-piperidinylfurano[3,2-d]pyrimidine.**

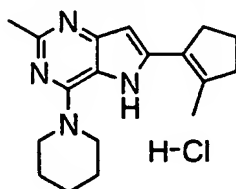
N,N-Dimethylpropionamide (0.15 mL, 1.35 mmol) was added dropwise to POCl₃ (10 mL) and stirred at room temperature under nitrogen for 1 hour. To this solution was added the aminonitrile furan (Example 95(b)) (275 mg, 1.26 mmol), and the resulting solution was refluxed for 16 h. The reaction was allowed to cool to room temperature and the solvent was evaporated in vacuo to leave a residue. The residue was dissolved in piperidine (10 mL) and the mixture was heated at reflux for 16 h. The reaction was cooled to room temperature and taken up in EtOAc (150 mL). The organic layer was washed with saturated NaHCO₃ (3x100 mL), brine (100 mL) and dried over MgSO₄, filtered and evaporated at reduced pressure to give an oil. Chromatography on silica gel (25 % EtOAc/Hexanes) gave 200 mg (47 %) of a yellow solid. The furanylpurine (150 mg, 0.432 mmol) was dissolved in EtOAc (10 mL) and stirred rapidly as ethereal HCl (0.44 mL, 0.44 mmol, 1.0 M) was added dropwise, and the mixture immediately became cloudy. After 1 h, the product was filtered off and dried in a vacuum oven at 60 °C to give 160 mg (96% yield). Mp: > 288° C. ¹H NMR (CDCl₃, 400 MHz): δ 1.31 (t, 3, *J* =

7.52), 1.75 (6), 2.88 (q, $J = 7.5$), 4.17 (s, 4), 7.52 (s, 1), 7.66 (d, 2, $J = 8.8$), 8.11 (d, 2, $J = 8.5$). MS m/z 342(M+1). Anal. Calcd for $C_{19}H_{21}Cl_2N_3O$: C, 60.32; H, 5.60; N, 11.11; Cl, 18.74. Found: C, 60.04; H, 5.63; N, 11.00; Cl, 18.61.

Example 97**6-(tert-Butyl)-2-methyl-4-piperidylpyrrolo[3,2-d]****pyrimidine Hydrochloride Hydrate**

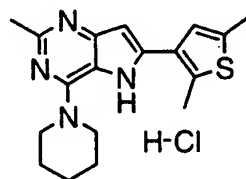
Using the method described in Example 30 by employing 1-(tert-butyl)vinylpyrrolidine (freshly prepared before use) (1.20 g, 7.73 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.60 g, 7.73 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (1.3 mL, 7.73 mmol), piperidine (Aldrich Chemical Company) (1.2 mL, 12.4 mmol), NEt_3 (Aldrich Chemical Company) (2.0 mL) and $SnCl_4$ (23 mL of a 2M solution in DMF). The crude residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$:MeOH as elutant to give 448 mg (21%) of the free base as a cream colored solid. 1H NMR ($DMSO-d_6$; 400 MHz): δ 1.36 (s, 9), 1.63 (br s, 6), 2.38 (s, 3), 3.60 (br s, 4), 6.05 (d, 1, $J = 1.6$), 10.20 (s, 1). MS m/z : 273 (M+1). To a hot solution of 6-(tert-butyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine (0.45 g, 1.65 mmol) in 10:1 EtOAc:MeOH (30 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.70 mL, 1.65 mmol). Crystallization occurred as the mixture cooled and the precipitate was collected by filtration, washed with Et_2O (3 x 10 mL) and dried under vacuum to

give 420 mg (83%) of the title compound as a white colored solid. Mp: 256-258 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.41 (s, 9), 1.67 (m, 6), 2.54 (s, 3), 3.98 (t, 4, J = 5.2), 6.26 (s, 1), 11.14 (s, 1), 14.32 (s, 2). MS m/z : 273 (M+1). Anal. Calcd for C₁₆H₂₅ClN₄•0.25H₂O: C, 61.41; H, 8.20; N, 17.91; Cl, 11.33. Found C, 61.41; H, 8.11; N, 17.90; Cl, 11.39.

Example 98**2-Methyl-6-(2-methylcyclopent-1-eneyl)-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.**

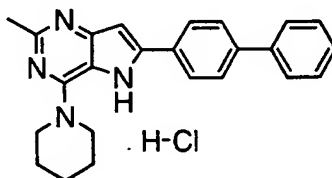
Using the method described in Example 30 by employing [1-(2-methylcyclopent-1-enyl)vinyl] pyrrolidine (freshly prepared before use) (2.41 g, 13.6 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.80 g, 13.6 mmol), *N,N*-diisopropyl ethyl amine (Aldrich Chemical Company) (2.4 mL, 13.6 mmol), piperidine (Aldrich Chemical Company) (2.1 mL, 21.7 mmol), NEt₃ (Aldrich Chemical Company) (2.0 mL) and SnCl₂ (41 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃:MeOH as elutant to give 552 mg (14%) of the free base as a pale yellow colored solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.62 (br s, 6), 1.85-1.90 (m, 2), 1.93 (s, 3), 2.39 (s, 3), 2.79 (br s, 2), 3.30 (br s, 2), 3.67 (br s, 4), 6.23 (s, 1), 10.36 (s, 1). MS m/z : 297 (M+1). To a hot solution of 2-methyl-6-(2-methylcyclopent-1-eneyl)-4-piperidylpyrrolo[3,2-d]pyrimidine (0.55 g, 1.86 mmol) in 5:1 EtOAc:MeOH (30 mL) was added 1M ethereal HCl (Aldrich Chemical

Company) (1.85 mL, 1.85 mmol). Crystallization occurred as the mixture cooled and the precipitate was collected by filtration, washed with EtOAc (1 x 5 mL), Et₂O (3 x 10 mL) and dried under vacuum to give 580 mg (94%) of the title compound as a white colored solid.
Mp: 224.5-226 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.69 (br s, 6), 1.89-1.93 (m, 5), 2.50 (s, 3), 2.82 (br s, 2), 3.31 (s, 2), 3.99 (br s, 4), 6.39 (s, 1), 11.49 (s, 1), 14.34 (s, 1). MS m/z : 297 (M+1). Anal. Calcd for C₁₈H₂₄N₄•HCl: C, 64.95; H, 7.57; N, 16.83; Cl, 10.65. Found C, 64.72; H, 7.63; N, 16.65; Cl, 10.37.

Example 99**15 2,5-Dimethyl-3-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)thiophene Hydrochloride Hydrate.**

Using the method described in Example 30 by employing 2,5-dimethyl-3-(1-pyrrolidinylvinyl) thiophene (freshly prepared before use) (1.40 g, 6.76 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.40 g, 6.76 mmol), *N,N*-diisopropyl ethyl amine (Aldrich Chemical Company) (1.2 mL, 6.76 mmol), piperidine (Aldrich Chemical Company) (1.1 mL, 10.8 mmol), NEt₃ (Aldrich Chemical Company) (1.0 mL) and SnCl₂ (20 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃:MeOH as elutant to give 335 mg (15%) of the free base as a beige colored solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.63 (br s, 6), 2.40 (s, 3), 2.42 (s, 3), 2.50 (s, 3), 3.70 (br s, 4), 6.36 (s, 1), 7.04 (s, 1), 10.82 (s, 1). MS m/z : 327 (M+1). To a hot solution of 2,5-dimethyl-3-(2-methyl-4-piperidyl

pyrrolo[4,5-d]pyrimidin-6-yl)thiophene (0.35 g, 1.02 mmol) in 5:1 EtOAc:MeOH (40 mL) was added 1M ethereal HCl (Aldrich Chemical Company) (1.00 mL, 1.00 mmol). Crystallization occurred as the mixture cooled and the precipitate was collected by filtration, washed with Et₂O (2 x 5 mL) and dried under vacuum to give 222 mg (60%) of the title compound as a beige colored solid. Mp: 240-241.5 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.70 (br s, 6), 2.44 (s, 3), 2.50 (s, 3), 2.55 (s, 3), 4.02 (br s, 4), 6.54 (s, 1), 7.06 (s, 1), 11.89 (s, 1), 14.15 (s, 1). MS m/z : 327 (M+1). Anal. Calcd for C₁₈H₂₂N₄S·HCl·1.5H₂O: C, 55.53; H, 6.68; N, 14.40; Cl, 9.00; S, 8.23. Found C, 55.62; H, 6.66; N, 14.31; Cl, 9.31; S, 8.28.

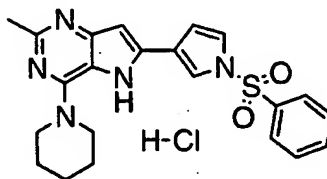


Example 100

2-Methyl-6-(4-phenylphenyl)-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

Using the method described in Example 30 by employing [1-(4-phenylphenyl)vinyl]pyrrolidine (freshly prepared before use) (1.35 g, 5.42 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.21 g, 5.42 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (0.9 mL, 5.42 mmol), piperidine (Aldrich Chemical Company) (0.9 mL, 8.67 mmol), NEt₃ (Aldrich Chemical Company) (1.0 mL) and SnCl₂ (Aldrich Chemical Company) (16 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃:MeOH as elutant to give 220 mg (11%) of the free base as a beige colored solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.67

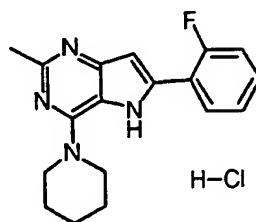
(br s, 6), 2.43 (s, 3), 3.74 (br s, 4), 6.80 (s, 1),
 7.39 (t, 1, $J = 7.2$), 7.50 (t, 2, $J = 7.7$), 7.75 (d,
 2, $J = 7.5$), 7.78 (d, 2, $J = 7.6$), 8.00 (d, 2, $J =$
 8.2), 11.01 (s, 1). MS m/z : 369 (M+1). To a hot
 5 solution of 2-methyl-6-(4-phenylphenyl)-4-piperidyl
 pyrrolo[3,2-d]pyrimidine (0.22 g, 0.59 mmol) in 10:1
 EtOAc: MeOH (40 mL) was added 1N ethereal HCl (Aldrich
 Chemical Company) (600 mL, 0.60 mmol). Crystallization
 occurred as the mixture cooled and the precipitate was
 10 collected by filtration, washed with Et₂O (3 x 5 mL)
 and dried under vacuum to give 205 mg (86%) of the
 title compound as a pale yellow colored solid. Mp:
 >280 °C. ¹H NMR (DMSO-*d*₆; 500 MHz): δ 1.72 (br s, 6),
 2.58 (s, 3), 4.07 (br s, 4), 6.96 (s, 1), 7.43 (t, 1,
 15 $J = 7.2$), 7.42 (t, 2, $J = 7.7$), 7.77 (d, 2, $J = 7.9$),
 7.86 (d, 2, $J = 8.1$), 8.06 (d, 2, $J = 8.1$), 12.00 (s,
 1), 14.29 (s, 1). MS m/z : 369 (M+1). Anal. Calcd
 for C₂₄H₂₄ N₄•HCl•1.0H₂O: C, 67.92; H, 6.45; N, 13.21;
 Cl, 8.35. Found C, 67.92; H, 6.43; N, 13.17; Cl,
 20 8.46.

Example 101

3-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)-
 25 **1-(phenylsulfonyl)pyrrole Hydrochloride Hydrate.**

Using the method described in Example 30 by
 employing 1-(phenylsulfonyl)-3-(1-pyrrolidinylvinyl)
 pyrrole (freshly prepared before use) (0.97 g, 4.68
 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine
 30 (Example 76(b)) (1.41 g, 4.68 mmol), *N,N*-diisopropyl
 ethyl amine (Aldrich Chemical Company) (0.8 mL, 4.68
 mmol), piperidine (Aldrich Chemical Company) (0.7 mL,

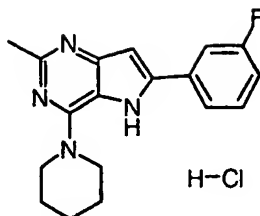
7.5 mmol), NEt_3 (Aldrich Chemical Company) (1.0 mL) and SnCl_2 (Aldrich Chemical Company) (14 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl_3 :MeOH as elutant to give 186 mg (9%) of the free base as a tan colored solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.64 (br s, 6), 2.38 (s, 3), 3.68 (br s, 4), 6.60 (s, 1), 6.92 (s, 1), 7.47 (s, 1), 7.68 (t, 2, $J = 7.5$), 7.77 (t, 1, $J = 7.5$), 8.00 (d, 2, $J = 7.6$), 8.09 (br s, 1), 10.74 (s, 1). MS m/z : 422 ($M+1$). To a hot solution of 3-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)-1-(phenylsulfonyl)pyrrole (0.18 g, 0.43 mmol) in 5:1 EtOAc: MeOH (40 mL) was added 1N etheral HCl (Aldrich Chemical Company) (432 mL, 0.43 mmol). Crystallization occurred as the mixture cooled and the precipitate was collected by filtration, washed with Et_2O (2 x 5 mL) and dried under vacuum to give 166 mg (85%) of the title compound as a brown colored powder. Mp: 183-185.5°C. ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.67 -1.69 (m, 6), 2.54 (s, 3), 4.02 (s, 4), 6.79 (s, 1), 7.06 (s, 1), 7.56 (t, 1, $J = 2.7$), 7.69 (t, 2, $J = 7.8$), 7.79 (t, 1, $J = 7.6$), 8.04 (d, 2, $J = 8.0$), 8.31 (s, 1), 11.70 (s, 1), 14.14 (s, 1). MS m/z : 422 ($M+1$). Anal. Calcd for $\text{C}_{22}\text{H}_{23}\text{N}_5\text{O}_2\text{S}\cdot\text{HCl}\cdot 1.5\text{H}_2\text{O}$: C, 54.26; H, 5.63; N, 14.39; Cl, 7.28. Found C, 54.31; H, 5.39; N, 13.99; Cl, 7.58.

**Example 102**

6-(2-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate

Using the method described in Example 30 by employing [1-(2-fluorophenyl)vinyl]pyrrolidine (freshly prepared before use) (1.02 g, 5.34 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.10 g, 5.34 mmol), *N,N*-diisopropylethyl amine (Aldrich Chemical Company) (1.3 mL, 7.73 mmol), piperidine (Aldrich Chemical Company) (0.9 mL, 5.34 mmol), *NEt*₃ (Aldrich Chemical Company) (1.0 mL) and *SnCl*₂ (Aldrich Chemical Company) (16 mL of a 2M solution in DMF). The residue was purified by flash chromatography on silica gel with 95:5 *CHCl*₃:MeOH as elutant to give 142 mg (9%) of the free base as a cream colored solid. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.65 (br s, 6), 2.43 (s, 3), 3.73 (br s, 4), 6.63 (s, 1), 7.33 (br s, 3), 7.44 (br s, 1), 7.87 (s, 1), 11.04 (s, 1). MS *m/z* : 311 (*M*+1). To a hot solution of 6-(2-fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*dl*]pyrimidine (0.14 g, 0.46 mmol) in 5:1 EtOAc:MeOH (30 mL) was added 1*N* etheral HCl (Aldrich Chemical Company) (460 mL, 0.46 mmol). Crystallization occurred as the mixture cooled and the precipitate was collected by filtration, washed with Et₂O (3 x 10 mL) and dried under vacuum to give 140 mg (88%) of the title compound as white colored long needles. Mp: 287-289 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.72 (br s, 6), 2.58 (s, 3), 4.05 (br s, 4), 6.80 (d, 1, *J* = 1.6), 7.39-7.46 (m, 2), 7.57 (q, 1, *J* = 7.1), 7.89 (t, 1, *J* = 7.7), 12.13 (s, 1), 14.37 (s, 1). MS *m/z* : 311 (*M*+1). Anal. Calcd for C₁₈H₁₉FN₄•HCl•H₂O: C, 59.28; H, 6.08; N, 15.37; Cl, 9.72. Found C, 59.28; H, 6.02; N, 15.39; Cl, 9.77.

195

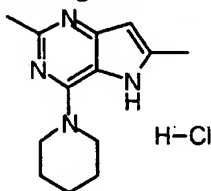
**Example 103****6-(3-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate**

- 5 Using the method described in Example 30 by
employing [1-(3-fluorophenyl)vinyl]pyrrolidine
(freshly prepared before use) (1.10 g, 5.81 mmol), 2-
methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b))
(1.21 g, 5.81 mmol), *N,N*-diisopropylethyl amine
10. (Aldrich Chemical Company) (0.9 mL, 5.81 mmol),
piperidine (Aldrich Chemical Company) (0.9 mL, 9.3
mmol), NEt_3 (Aldrich Chemical Company) (1.0 mL) and
 SnCl_2 (Aldrich Chemical Company) (17 mL of a 2M
solution in DMF). The residue was purified by flash
15 chromatography on silica gel with 95:5 CHCl_3 :MeOH as
elutant to give 82 mg (5%) of the free base as a beige
colored solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.65 (br
s, 4), 2.42 (s, 3), 3.72 (br s, 4), 6.85 (s, 1), 7.22
(m, 1), 7.51 (m, 1), 7.75-7.81 (m, 2), 10.97 (s, 1).
20 MS m/z : 311 ($M+1$). To a hot (near boiling) solution
of 6-(3-fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-
d]pyrimidine (82.0 mg, 0.26 mmol) in 10:1 EtOAc: MeOH
(30 mL) was added 1M ethereal HCl (Aldrich Chemical
Company) (265 mL, 0.26 mmol). Crystallization
25 occurred as the mixture cooled and the precipitate was
collected by filtration, washed with Et_2O (2 x 5 mL)
and dried under vacuum to give 82 mg (91%) of the
title compound as beige colored small needles. Mp:
>285 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.71 (br s, 6),
30 2.57 (s, 3), 4.06 (br s, 4), 6.99 (s, 1), 7.35 (t, 1,
 $J = 8.5$), 7.60 (q, 1, $J = 7.7$), 7.83 (d, 1, $J = 7.6$),

196

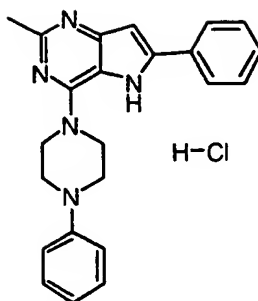
7.91 (d, 1, $J = 10.2$), 11.99 (s, 1), 14.34 (s, 1). MS m/z : 311 (M+1). Anal. Calcd for $C_{18}H_{19}FN_4 \cdot HCl \cdot H_2O$: C, 59.17; H, 6.09; N, 15.34; Cl, 9.70. Found C, 59.17; H, 6.09; N, 15.21; Cl, 9.81.

5

Example 104**2,6-Dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

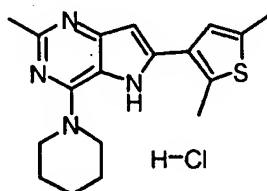
- 10 This compound was prepared according to the method described in Example 46(e) by employing 2,6-dimethyl-4-chloro-5H-pyrrolo[3,2-d]pyrimidine (Example 46(d)) (0.29 g, 1.60 mmol) with piperidine (Aldrich Chemical Company) (0.80 mL, 8.1 mmol) and K_2CO_3 (0.58 g, 4.7 mmol) in H_2O (6.0 mL). The hydrochloride salt was formed by treating a CH_2Cl_2 solution of the crude product with ethereal HCl (1.0 M, 1.1 mL, 1.1 mmol). Recrystallization from MeOH gave 0.090g (21%) of the title compound as a hygroscopic beige solid. Mp: 244-245.5 °C. 1H NMR ($DMSO-d_6$; 500 MHz): δ 1.67 (m, 4), 1.72 (m, 2), 2.48 (s, 3), 2.52 (s, 3), 3.97 (t, 4), 6.30 (s, 1), 6.18 (s, 1), 11.92 (s, 1), 14.00 (s, 1); MS m/z : 231 (M+1). Anal. Calcd for $C_{13}H_{18}N_4 \cdot 1.05HCl \cdot 0.86H_2O$: C, 54.94; H, 7.37; N, 19.72; Cl, 13.11.
- 20 Found: C, 54.94; H, 7.57; N, 19.36; Cl, 13.14.
- 25

197

**Example 105****2-Methyl-6-phenyl-4-(4-phenylpiperazinyl)pyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

5 A mixture of 2-methyl-4-chloro-6-phenyl-5H-pyrrolo [3,2-d]pyrimidine (Example 1(e)) (0.51 g, 2.45 mmol) and 1-phenylpiperazine (Aldrich Chemical Company) (10 mL) was stirred at 140 °C for 4 h under a N₂ atmosphere. After cooling the precipitate was removed by filtration ,
10 and the filtrate was poured onto a mixture of CH₂Cl₂ (30 mL) and H₂O (40 mL). The mixture was transferred to a separatory funnel where the organic solution was collected, washed with H₂O (3 x 40 mL), saturated NaCl (50 mL), dried (MgSO₄), filtered and concentrated under
15 reduced pressure. The residue was purified by flash chromatography on silica gel with 97:3 CHCl₃/MeOH as eluant to give 483 mg (54%) of 2-methyl-6-phenyl-4-(4-phenylpiperazinyl)pyrrolo[3,2-d]pyrimidine as a tan colored solid. This compound (483 mg, 1.31 mmol) was
20 dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.30 mL, 1.30 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 5 mL),
25 Et₂O (2 x 5 mL) and dried under vacuum at 60 °C to give 404 mg (41%) of the title compound as a beige powder. Mp: 232-234.5 °C. ¹H NMR (DMSO-d₆; 500 MHz): δ 2.55 (s, 3), 3.36 (br s, 4), 4.21 (br s, 4), 6.80 (t, 1, J = 7.2), 6.88 (s, 1), 6.99 (d, 2, J = 7.8), 7.22 (t, 2, J

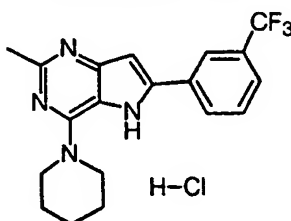
= 7.5), 7.46 (q, 1, $J = 7.1$), 7.51 (t, 2, $J = 7.3$),
7.93 (d, 2, $J = 7.7$), 12.06 (s, 1), 14.46 (s, 1). MS
 m/z : 370 ($M+1$ for free base). Anal. Calcd for
 $C_{23}H_{23}N_5 \cdot 2.0HCl \cdot 2.5H_2O$: C, 56.67; H, 6.20; N, 14.37; Cl,
5 14.55. Found: C, 56.67; H, 6.23; N, 14.19; Cl, 14.34.

Example 106

10 **2,5-Dimethyl-3-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]thiophene Hydrochloride Hydrate.**

Using the method described in Example 30 by
employing 2,5-dimethyl-3-(1-pyrrolidinylvinyl)thiophene
(freshly prepared from 3-acetyl-2,5-dimethylthiophene
(Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (1.40
15 g, 6.76 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine
(Example 76(b)) (1.40 g, 6.76 mmol), *N,N*-diisopropyl
ethylamine (1.2 mL, 6.76 mmol), piperidine (1.1 mL,
10.8 mmol), NEt_3 (1.2 mL) and $SnCl_4$ (20 mL of a 2 M soln
in DMF). The residue was purified by flash
20 chromatography on silica gel with 95:5 $CHCl_3/MeOH$ as
eluant to give 335 mg (15%) of 2,5-dimethyl-3-[2-
methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]
thiophene as a tan colored solid. This material (335
mg, 1.00 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL)
25 and heated to boiling. To the hot solution was added 1
M ethereal HCl (1.00 mL, 1.00 mmol). The solution was
left to cool to room temperature. The resulting
crystals were collected by filtration, washed with
EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under
30 vacuum at 60 °C to give 222 mg (9%) of the title
compound as a beige colored solid. Mp: 240-241.5 °C.
 1H NMR ($DMSO-d_6$; 400 MHz): δ 1.70 (br s, 6), 2.44 (s,

3), 2.50 (s, 3), 2.55 (s, 3), 4.02 (br s, 4), 6.54 (s, 1), 7.06 (s, 1), 11.89 (s, 1), 14.15 (s, 1). MS m/z : 327 ($M+1$ for free base). Anal. Calcd for $C_{18}H_{22}N_4S \cdot HCl \cdot 1.5H_2O$: C, 55.53; H, 6.68; N, 14.40; Cl, 9.00; S, 8.23. Found: C, 55.62; H, 6.66; N, 14.31; Cl, 9.13; S, 8.28.

Example 107

10 **2-Methyl-4-piperidyl-6-[3-(trifluoromethyl)phenyl]
pyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.**

Using the method described in Example 30 by employing [1-(3-(trifluoromethyl)phenyl)vinyl]pyrrolidine (freshly prepared before use from 3-(trifluoromethyl)acetophenone (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (1.97 g, 8.17 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.70 g, 8.17 mmol), *N,N*-diisopropylethylamine (1.4 mL, 8.17 mmol), piperidine (1.3 mL, 13.1 mmol), NEt_3 (1.3 mL) and $SnCl_4$ (25 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$ /MeOH as eluant to give 500 mg (17%) of 2-methyl-4-piperidyl-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidine as a beige colored solid.

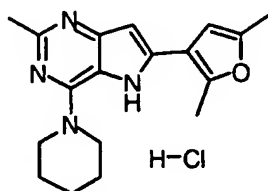
25 This material (500 mg, 1.39 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.40 mL, 1.40 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by

30 filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 493 mg

(15%) of the title compound as a white colored solid.

Mp: 241-243 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.72 (br s, 6), 2.59 (s, 3), 4.08 (s, 4), 7.14 (s, 1), 7.79 (t, 1, J = 7.6), 7.85 (d, 1, J = 7.5), 8.30 (d, 1, J = 7.6), 8.34 (s, 1), 12.92 (s, 1), 14.53 (s, 1). MS m/z: 361 (M+1 for free base). Anal. Calcd for C₁₉H₁₉F₃N₄•HCl•1.0H₂O: C, 55.00; H, 5.35; N, 13.51; Cl, 8.55. Found: C, 54.99; H, 5.20; N, 13.39; Cl, 8.60.

10

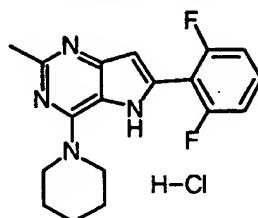
Example 108**2,5-Dimethyl-3-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)furan Hydrochloride Monohydrate.**

Using the method described in Example 30 by
15 employing 2,5-dimethyl-3-[1-pyrrolidinyl]furan (freshly prepared before use from 3-acetyl-2,5-dimethylfuran (Aldrich Chemical Company), pyrrolidine and TiCl₄ (4.88 g, 25.5 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (5.30 g, 25.5 mmol), *N,N*-diisopropyl
20 ethylamine (4.5 mL, 25.5 mmol), piperidine (4.0 mL, 40.8 mmol), NEt₃ (4.0 mL) and SnCl₂ (77 mL of a 2 M soln in DMF). Note because of the increase in scale, the workup involved NaOH (15 g) and crushed ice (300 mL). The residue was purified by flash chromatography on
25 silica gel with 95:5 CHCl₃/MeOH as eluant to give 1.01 g (13%) of 2,5-dimethyl-3-(2-methyl-4-piperidylpyrrolo [4,5-d]pyrimidin-6-yl)furan as a beige colored powder. This material (1.01 g, 3.22 mmol) was dissolved in 2:1 EtOAc/MeOH (100 mL) and heated to boiling. To the hot
30 solution was added 1 M ethereal HCl (3.25 mL, 3.25 mmol). The solution was left to cool to room

temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 878 mg (10%) of the title compound as a white colored solid.

5 Mp: 238-240 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.69 (br s, 6), 2.29 (s, 3), 2.44 (s, 3), 2.55 (s, 3), 4.01 (s, 4), 6.47 (s, 1), 6.55 (s, 1), 11.67 (s, 1), 14.18 (s, 1). MS *m/z*: 311 (*M*+1 for free base). Anal. Calcd for C₁₈H₂₂N₄O•HCl•1.0H₂O: C, 59.25; H, 6.91; N, 15.36; Cl, 9.72. Found: C, 59.19; H, 6.80; N, 15.30; Cl, 9.88.

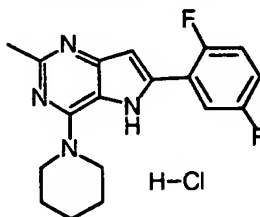
Example 109



6-(2,6-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d] pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing [1-(2,6-difluorophenyl)vinyl]pyrrolidine (freshly prepared before use from 2',6'-difluoro acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.51 g, 7.22 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.20 g, 5.79 mmol), *N,N*-diisopropylethylamine (1.3 mL, 7.22 mmol), piperidine (1.2 mL, 11.6 mmol), NEt₃ (1.2 mL) and SnCl₂ (22 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 199 mg (11%) of 6-(2,6-difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a beige colored powder. This material (199 mg, 0.61 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.60 mL, 0.60 mmol). The

solution was left to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 33 mg (2%) of the title compound as a pale yellow colored sandy solid. Mp: >280 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.71 (br s, 6), 2.58 (s, 3), 4.02 (s, 4), 6.77 (s, 1), 7.35 (t, 2, *J* = 8.3), 7.67 (dq, 1, *J* = 1.4, 6.8), 12.41 (s, 1), 14.51 (s, 1). MS *m/z*: 329 (*M*+1 for free base). Anal. Calcd for C₁₈H₁₈F₂N₄•HCl•1.2H₂O: C, 55.99; H, 5.58; N, 14.51; Cl, 9.18. Found: C, 55.99; H, 5.61; N, 14.41; Cl, 9.08.

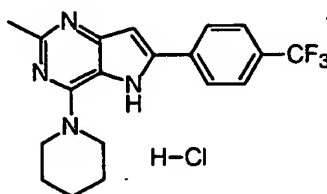
Example 110

15

6-(2,5-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

Using the method described in Example 30 by employing [1-(2,5-difluorophenyl)vinyl]pyrrolidine (freshly prepared before use from 2',5'-difluoro acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.45 g, 6.94 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.00 g, 4.83 mmol), *N,N*-diisopropylethylamine (1.2 mL, 6.94 mmol), piperidine (1.1 mL, 11.1 mmol), NEt₃ (1.2 mL) and SnCl₄ (21 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 417 mg (26%) of 6-(2,5-difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a tan colored foam. This material (415 mg, 1.25 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL)

and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.30 mL, 1.30 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 337 mg (19%) of the title compound as white colored needles. Mp: 279-281 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.71 (br s, 6), 2.58 (s, 3), 4.06 (s, 4), 6.85 (s, 1), 7.42-7.55 (m, 2), 7.86-7.91 (m, 1), 12.13 (s, 1), 14.41 (s, 1). MS *m/z*: 329 (M+1 for free base). Anal. Calcd for C₁₈H₁₆F₃N₄•HCl•1.0H₂O: C, 56.54; H, 5.50; N, 14.65. Found: C, 56.29; H, 5.61; N, 14.53.

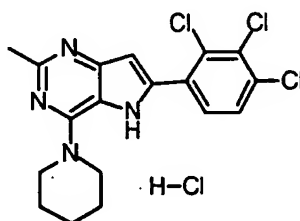


Example 111

2-Methyl-4-piperidyl-6-[4-(trifluoromethyl)phenyl]pyrrolo[3,2-*d*]pyrimidine hydrochloride Hydrate.

Using the method described in Example 30 by employing [1-[4-(trifluoromethyl)phenyl]vinyl]pyrrolidine (freshly prepared before use from 4-(trifluoromethyl) acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.21 g, 5.02 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.00 g, 5.02 mmol), *N,N*-diisopropylethylamine (0.9 mL, 5.02 mmol), piperidine (0.8 mL, 8.0 mmol), NEt₃ (1.0 mL) and SnCl₂ (15 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 248 mg (14%) of 2-methyl-4-piperidyl-6-[4-(trifluoromethyl)phenyl]pyrrolo[3,2-*d*]pyrimidine as a beige colored solid.

This material (245 mg, 0.69 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.70 mL, 0.70 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 187 mg (10%) of the title compound as a beige colored solid. Mp: 278-280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.72 (br s, 6), 2.58 (s, 3), 4.08 (s, 4), 7.05 (s, 1), 7.93 (d, 2, J = 8.3), 8.20 (d, 2, J = 8.2), 12.16 (s, 1), 14.32 (s, 1). MS m/z: 361 (M+1 for free base). Anal. Calcd for C₁₉H₁₉F₃N₄•HCl•1.5H₂O: C, 53.79; H, 5.43; N, 13.21; Cl, 8.26. Found: C, 54.01; H, 5.40; N, 13.18; Cl, 8.60.

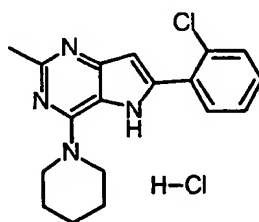


Example 112

2-Methyl-4-piperidyl-6-(2,3,4-trichlorophenyl)pyrrolo [3,2-d]pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing [1-(2,3,4-trichlorophenyl)vinyl]pyrrolidine (freshly prepared before use from 2',3',4'-trichloro acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.00 g, 3.64 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (0.80 g, 3.64 mmol), N,N-diisopropylethylamine (0.6 mL, 3.64 mmol), piperidine (0.6 mL, 5.80 mmol), NEt₃ (0.7 mL) and SnCl₂ (11 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 125 mg (9%) of 2-methyl-4-

piperidyl-6-(2,3,4-trichlorophenyl)pyrrolo[3,2-d]pyrimidine as a brown colored oil. This material (125 mg, 0.32 mmol) was dissolved in 5:1 EtOAc/MeOH (15 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.40 mL, 0.40 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 55 mg (4%) of the title compound as beige colored needles. Mp: 264-266 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.71 (br s, 6), 2.58 (s, 3), 4.03 (s, 4), 6.78 (s, 1), 7.71 (d, 2, J = 8.4), 7.88 (d, 2, J = 8.5), 12.40 (s, 1), 14.39 (s, 1). MS m/z: 396 (M+1 for free base). Anal. Calcd for C₁₈H₁₇Cl₃N₄•HCl•1.75H₂O: C, 46.59; H, 4.67; N, 12.09; Cl, 30.59. Found: C, 46.64; H, 4.60; N, 11.93; Cl, 30.48.



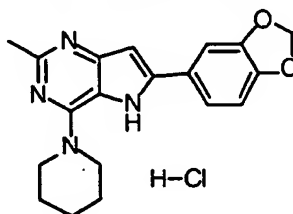
Example 113

2-Methyl-4-piperidyl-6-(2-chlorophenyl)pyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

Using the method described in Example 30 by employing [1-(2-chlorophenyl)vinyl]pyrrolidine (freshly prepared before use from 2'-chloro acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.06 g, 5.12 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.10 g, 5.12 mmol), N,N-diisopropylethylamine (0.9 mL, 5.12 mmol), piperidine (0.8 mL, 8.2 mmol), NEt₃ (0.9 mL) and SnCl₄ (15 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with

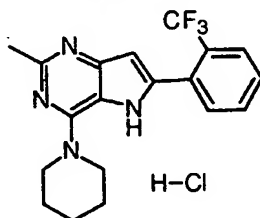
95:5 CHCl₃/MeOH as eluant to give 442 mg (25%) of 2-methyl-4-piperidyl-6-(2-chlorophenyl)pyrrolo[3,2-d]pyrimidine as a brown colored solid. This material (450 mg, 1.37 mmol) was dissolved in 5:1 EtOAc/MeOH (35 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.40 mL, 1.40 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 343 mg (17%) of the title compound as brown colored needles. Mp: 240-241.5 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.71 (br s, 6), 2.59 (s, 3), 4.03 (s, 4), 6.74 (s, 1), 7.55 (dq, 2, J = 1.3, 7.8), 7.70 (dt, 2, J = 0.9, 8.2), 12.34 (s, 1), 14.64 (s, 1). MS m/z: 327 (M+1 for free base). Anal. Calcd for C₁₈H₁₉ClN₄•HCl•H₂O: C, 56.70; H, 5.82; N, 14.70; Cl, 18.59. Found: C, 56.93; H, 5.91; N, 14.63; Cl, 18.70.

20

Example 114**5-[2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-2H-benzo[d]1,3-dioxolane Hydrochloride Monohydrate.**

Using the method described in Example 30 by employing 5-[1-pyrrolidinylvinyl]-2H-benzo[d]1,3-dioxane (freshly prepared before use from 3',4'-(methylenedioxy)acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.17 g, 5.39 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.10 g, 5.40 mmol), N,N-diisopropylethylamine (1.0 mL, 5.40 mmol), piperidine (0.9 mL, 8.6 mmol), NEt₃,

(0.9 mL) and SnCl_2 (16 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 397 mg (22%) of 5-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-2H-benzo[d]1,3-dioxolane as a beige colored solid. This material (398 mg, 1.18 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.20 mL, 1.20 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 266 mg (13%) of the title compound as a beige colored powder. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.71 (br s, 6), 2.56 (s, 3), 4.04 (s, 4), 6.14 (s, 2), 6.83 (s, 1), 7.11 (d, 1, $J = 8.2$), 7.52 (d, 1, $J = 8.2$), 7.61 (s, 1), 11.82 (s, 1), 14.37 (s, 1). MS m/z : 337 ($M+1$ for free base). Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_2 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 58.38; H, 5.93; N, 14.34; Cl, 9.07. Found: C, 58.01; H, 6.00; N, 14.19; Cl, 8.94.

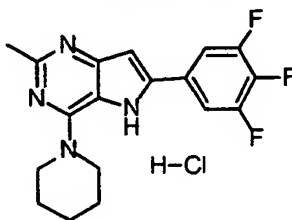
Example 115

2-Methyl-4-piperidyl-6-[2-(trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

Using the method described in Example 30 by employing [1-(2-(trifluoromethyl)phenyl)vinyl]pyrrolidine (freshly prepared before use from 2-(trifluoromethyl)acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl_4 (1.19 g, 4.94 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b))

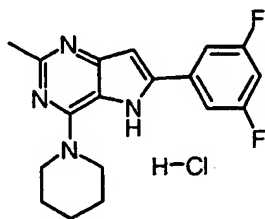
(1.00 g, 4.94 mmol), *N,N*-diisopropylethylamine (0.9 mL, 4.94 mmol), piperidine (0.8 mL, 7.9 mmol), *NEt*₃ (0.9 mL) and *SnCl*₂ (15 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with 95:5 *CHCl*₃/*MeOH* as eluant to give 330 mg (19%) of 2-methyl-4-piperidyl-6-[2-(trifluoromethyl)phenyl]pyrrolo[3,2-*d*]pyrimidine as a tan colored solid. This material (330 mg, 0.90 mmol) was dissolved in 5:1 *EtOAc/MeOH* (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal *HCl* (0.90 mL, 0.90 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by filtration, washed with *EtOAc* (2 x 10 mL), *Et*₂*O* (3 x 15 mL) and dried under vacuum at 60 °C to give 202 mg (11%) of the title compound as beige colored cube shaped crystals. *Mp*: >280 °C. ¹*H* NMR (*DMSO-d*₆; 400 MHz): δ 1.70 (br s, 6), 2.58 (s, 3), 4.01 (s, 4), 6.62 (s, 1), 7.74 (d, 1, *J* = 7.5), 7.79 (t, 1, *J* = 7.5), 7.86 (t, 1, *J* = 7.4), 7.97 (d, 1, *J* = 7.8), 12.45 (s, 1), 14.43 (s, 1). *MS m/z*: 361 (*M*+1 for free base). *Anal.* Calcd for *C*₁₉*H*₁₉*F*₃*N*₄•*HCl*•*H*₂*O*: *C*, 55.00; *H*, 5.35; *N*, 13.51; *Cl*, 8.55. Found: *C*, 55.25; *H*, 5.41; *N*, 13.31; *Cl*, 8.76.

25

Example 116**2-Methyl-4-piperidyl-6-(3,4,5-trifluorophenyl)pyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.**

Using the method described in Example 30 by employing [1-(3,4,5-trifluorophenyl)vinyl]pyrrolidine (freshly prepared before use from 3,4,5-trifluoro

acetophenone (Oakwood Products Inc.), pyrrolidine and TiCl_4 (1.58 g, 6.96 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.40 g, 6.96 mmol), *N,N*-diisopropylethylamine (1.2 mL, 6.96 mmol),
5 piperidine (1.1 mL, 11.1 mmol), NEt_3 (1.1 mL) and SnCl_2 (21 mL of a 2 M soln in DMF). In this example the 2 M SnCl_2 solution was added to the reaction mixture at 140 °C. Heating was then discontinued and the mixture was allowed to cool to room temperature. The mixture was
10 stirred at room temperature for an additional 48 h. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 620 mg (26%) of 2-methyl-4-piperidyl-6-(3,4,5-trifluorophenyl)pyrrolo[3,2-*d*]pyrimidine as a beige colored
15 gummy solid. This compound (621 mg, 1.80 mmol) was dissolved in 3:1 EtOAc/MeOH (50 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.80 mL, 1.80 mmol). The solution was allowed to cool to room temperature. The resulting crystals were
20 collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 426 mg (16%) of the title compound as a white colored fluffy solid. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.71 (br s, 6), 2.58 (s, 3), 4.07 (s, 4),
25 7.07 (s, 1), 8.14 (m, 2), 12.04 (s, 1), 14.45 (s, 1). MS *m/z*: 347 (*M*+1 for free base). Anal. Calcd for $\text{C}_{18}\text{H}_{17}\text{F}_3\text{N}_4 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 55.23; H, 4.88; N, 14.32; Cl, 9.06. Found: C, 55.23; H, 4.86; N, 14.11; Cl, 9.06.

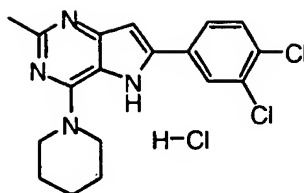


Example 117

6-(3,5-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

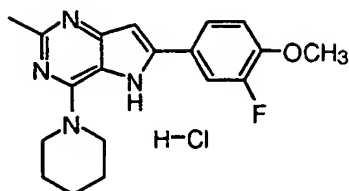
Using the method described in Example 30 by employing 1-(3,5-difluorophenyl)vinylpyrrolidine (freshly prepared before use from 3,5-difluoro acetophenone (Oakwood Products Inc.), pyrrolidine and TiCl_4 (1.32 g, 6.32 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.30 g, 6.32 mmol), *N,N*-diisopropylethylamine (1.1 mL, 6.32 mmol), piperidine (1.0 mL, 10.1 mmol), NEt_3 (1.1 mL) and SnCl_4 (19 mL of a 2 M soln in DMF). In this example the 2 M SnCl_4 solution was added to the reaction mixture at 140 °C. Heating was then discontinued and the mixture was allowed to cool to room temperature. The mixture was stirred at room temperature for an additional 48 h. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 820 mg (40%) of 6-(3,5-difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a brown colored gummy solid. This compound (820 mg, 2.52 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (2.50 mL, 2.50 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 440 mg (19%) of the title compound as pale yellow colored needles. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.61 (br s, 6), 2.47 (s, 3), 3.97 (br s, 4), 6.97 (s, 1), 7.28 (tt, 1, $J = 2.1, 7.1$), 7.74 (d, 2, $J = 6.6$), 11.93 (s, 1), 14.35 (s, 1). MS m/z : 329 ($M+1$ for free base). Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{F}_2\text{N}_4 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 56.47; H, 5.53; N, 14.64; Cl, 9.26. Found: C, 56.52; H, 5.54; N, 14.74; Cl, 9.38.

211

**Example 118****6-(3,4-Dichlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.**

5 Using the method described in Example 30 by
employing [1-(3,5-dichlorophenyl)vinyl]pyrrolidine
(freshly prepared before use from 3',4'-dichloro
acetophenone (Aldrich Chemical Company), pyrrolidine
and TiCl_4 (1.09 g, 4.50 mmol), 2-methyl-4,6-dichloro-5-
10 nitropyrimidine (Example 76(b)) (0.90 g, 4.50 mmol),
N,N-diisopropylethylamine (0.8 mL, 4.50 mmol),
piperidine (0.7 mL, 7.2 mmol), NEt_3 (0.7 mL) and SnCl_4
(14 mL of a 2 M soln in DMF). The residue was purified
by flash chromatography on silica gel with 95:5
15 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 86 mg (5%) of 6-(3,4-
dichlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]
pyrimidine as a tan colored oil. This material (86 mg,
0.24 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and
heated to boiling. To the hot solution was added 1 M
20 ethereal HCl (250 mL, 0.24 mmol). The solution was
left to cool to room temperature. The resulting
crystals were collected by filtration, washed with
EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under
vacuum at 60 °C to give 31 mg (2%) of the title
25 compound as a brown colored solid. Mp: 265-268 °C. ^1H
NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.71 (br s, 6), 2.57 (s, 3),
4.02 (s, 4), 7.06 (s, 1), 7.83 (d, 1, $J = 8.3$), 8.00
(dd, 1, $J = 1.7, 8.5$), 8.34 (d, 1, $J = 1.7$), 12.04 (s,
1), 14.32 (s, 1). MS m/z : 361 ($M+1$ for free base).
30 Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{Cl}_2\text{N}_4 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 52.00; H, 5.09; N,

13.48; Cl, 25.58. Found: C, 51.65; H, 5.00; N, 13.24; Cl, 25.49.



5 **Example 119**

2-Fluoro-1-methoxy-4-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzene Hydrochloride Hydrate.

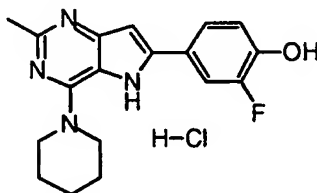
Using the method described in Example 30 by employing 2-fluoro-1-methoxy-4-(1-pyrrolidinylvinyl) benzene (freshly prepared before use from 3-fluoro-4-methoxyacetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.37 g, 6.19 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.30 g, 6.19 mmol), *N,N*-diisopropylethylamine (1.1 mL, 6.19 mmol), piperidine (1.0 mL, 9.9 mmol), NEt₃ (1.1 mL) and SnCl₂ (19 mL of a 2 M soln in DMF). In this example the 2 M SnCl₂ solution was added to the reaction mixture at 140 °C. Heating was then discontinued and the mixture was allowed to cool to room temperature.

20 The mixture was stirred at room temperature for an additional 48 h. The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 481 mg (23%) of 2-fluoro-1-methoxy-4-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzene as a beige colored solid. This compound (481 mg, 1.41 mmol) was dissolved in 4:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.40 mL, 1.40 mmol). The solution was allowed to cool to room temperature. The resulting

30 crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 372 mg (16%) of the title

compound as a beige colored solid. Mp: 262-264 °C. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.69 (br s, 6), 2.56 (s, 3), 3.92 (s, 3), 4.05 (br t, 4, J = 5.4), 6.59 (s, 1), 7.33 (t, 1, J = 8.8), 7.80 (d, 1, J = 8.6), 7.96 (dd, 1, J = 2.0, 12.7), 11.82 (s, 1), 14.20 (s, 1). MS m/z: 341 (M+1 for free base). Anal. Calcd for C₁₉H₂₁FN₄O•HCl•0.5H₂O: C, 59.08; H, 5.96; N, 14.51; Cl, 9.08. Found: C, 58.90; H, 5.89; N, 14.46; Cl, 9.30.

10

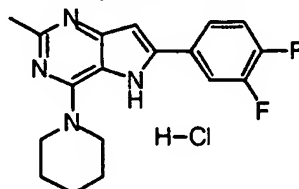
Example 120**2-Fluoro-4-[2-methyl-4-pyridylpyrrolo[4,5-d]pyrimidin-6-yl]phenol Hydrochloride Hydrate.**

To a -78 °C solution of 2-fluoro-1-methoxy-4-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzene (Example 119) (0.80 g, 2.35 mmol) in CH₂Cl₂ (40 mL) under a N₂ atmosphere was added 1 M BBr₃ (4.7 mL, 4.70 mmol). The reaction mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for an additional 20 h. The reaction mixture was then poured onto ice-water (200 mL) and the pH of the aqueous solution was adjusted to pH 9 with the addition of NEt₃ (4 mL). The resulting mixture was stirred at room temperature for 2 h. The solid which formed was removed by filtration and discarded. The remaining solution was transferred to a separatory funnel. The organic solution was separated, washed with H₂O (100 mL), saturated NaCl (100 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to afford 483 mg (62%) of 2-fluoro-4-(2-methyl-4-pyridylpyrrolo[4,5-d]pyrimidin-6-yl)phenol as

214

a pale yellow colored solid. This compound (481 mg, 1.50 mmol) was dissolved in 4:2:1 EtOAc/MeOH/CH₂Cl₂ (50 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.50 mL, 1.50 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 315 mg (37%) of the title compound as a pale yellow colored solid. Mp: >280 °C.

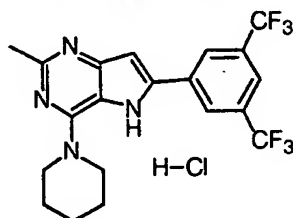
¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.63 (br s, 6), 2.49 (s, 3), 3.96 (br s, 4), 6.76 (s, 1), 7.06 (dt, 1, *J* = 1.9, 8.7), 7.58 (d, 1, *J* = 8.5), 7.83 (dd, 1, *J* = 1.9, 12.5), 10.47 (s, 1), 11.79 (s, 1), 14.12 (s, 1). MS *m/z*: 327 (*M*+1 for free base). Anal. Calcd for C₁₈H₁₉FN₄O•HCl•1.5H₂O: C, 55.45; H, 5.95; N, 14.37; Cl, 9.09. Found: C, 55.49; H, 5.87; N, 14.07; Cl, 9.03.

Example 121**20 6-(3,4-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

Using the method described in Example 30 by employing [1-(3,4-difluorophenyl)vinyl]pyrrolidine (freshly prepared before use from 3',4'-difluoro acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.38 g, 6.60 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.40 g, 6.60 mmol), *N,N*-diisopropylethylamine (1.1 mL, 6.60 mmol), piperidine (1.0 mL, 10.6 mmol), NEt₃ (1.1 mL) and SnCl₄ (20 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with 95:5

CHCl₃/MeOH as eluant to give 395 mg (18%) of 6-(3,4-difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine as a beige colored solid. This material (395 mg, 1.20 mmol) was dissolved in 10:1 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.20 mL, 1.20 mmol). The solution was left to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 159 mg (6%) of the title compound as beige colored solid. Mp: 243-245 °C. ¹H NMR (DMSO-*d*₆; 500 MHz): δ 1.71 (br s, 6), 2.57 (s, 3), 4.06 (t, 4, *J* = 5.0), 6.85 (s, 1), 7.63 (q, 1, *J* = 10.0), 7.89 (d, 1, *J* = 8.1), 8.19 (dt, 1, *J* = 1.3, 9.5), 12.01 (s, 1), 14.39 (s, 1). MS *m/z*: 329 (*M*+1 for free base). Anal. Calcd for C₁₈H₁₈F₂N₄•HCl•1.25H₂O: C, 55.81; H, 5.60; N, 14.47; Cl, 9.15. Found: C, 55.95; H, 5.25; N, 14.62; Cl, 9.26.

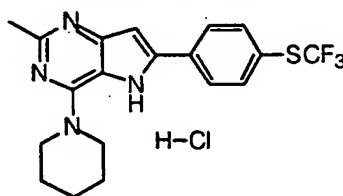
20

Example 122**6-((3,5-bis(Trifluoromethyl)phenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride.**

Using the method described in Example 30 by employing [1-(3,5-bis(trifluoromethyl)phenyl)vinyl]pyrrolidine (freshly prepared before use from 3',5'-bis(trifluoromethyl)acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.33 g, 4.30 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (0.90 g, 4.30 mmol), *N,N*-diisopropylethylamine (0.7 mL, 4.30 mmol), piperidine (0.7 mL, 6.90 mmol), NEt₃ (1.0

mL) and SnCl_4 (13 mL of a 2 M soln in DMF). The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 232 mg (13%) of 6-((3,5-bis(trifluoromethyl)phenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a brown colored oil. This material (232 mg, 0.54 mmol) was dissolved in 10:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.60 mL, 0.60 mmol). The solution was left to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 57 mg (3%) of the title compound as a beige colored solid. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.73 (br s, 6), 2.60 (s, 3), 4.10 (s, 4), 7.30 (s, 1), 8.22 (s, 1), 8.68 (s, 2), 12.27 (s, 1), 14.43 (s, 1). MS m/z : 429 (M+1 for free base). Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{F}_6\text{N}_4 \cdot \text{HCl}$: C, 51.68; H, 4.12; N, 12.05; Cl, 7.63. Found: C, 51.51; H, 4.17; N, 11.96; Cl, 7.82.

20

Example 123

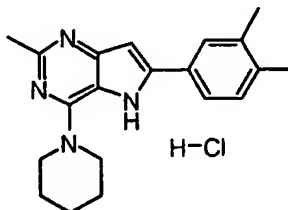
Trifluoro[4-(2-methyl-4-piperidylpyrrolo[4;5-d]pyrimidin-6-yl)phenylthio]methane Hydrochloride Monohydrate.

25

Using the method described in Example 30 by employing trifluoro[4-(1-pyrrolidinylvinyl)phenylthio]methane (freshly prepared before use from 4'-(trifluoromethylthio)acetophenone (Oakwood Products Inc.), pyrrolidine and TiCl_4 (1.96 g, 7.17 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.50 g,

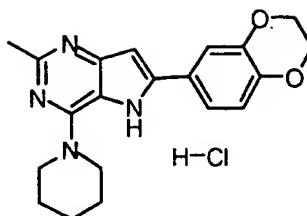
30

7.17 mmol), *N,N*-diisopropylethylamine (1.2 mL, 7.17 mmol), piperidine (1.1 mL, 11.5 mmol), NEt_3 (1.1 mL) and SnCl_4 (21 mL of a 2 M soln in DMF). In this example the SnCl_4 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 742 mg (26%) of trifluoro[4-(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenylthio]methane as a beige colored foam. This compound (741 mg, 1.90 mmol) was dissolved in 10:1 EtOAc/MeOH (60 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.90 mL, 1.90 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 418 mg (13%) of the title compound as white colored needles. Mp: 270-272 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.65 (br s, 6), 2.51 (s, 3), 4.00 (br s, 4), 6.96 (s, 1), 7.84 (d, 2, $J = 8.1$), 8.06 (d, 2, $J = 8.2$), 12.12 (s, 1), 14.39 (s, 1). MS m/z : 393 ($M+1$ for free base). Anal. Calcd for $\text{C}_{19}\text{H}_{19}\text{F}_3\text{N}_4\text{S}\cdot\text{HCl}\cdot\text{H}_2\text{O}$: C, 51.06; H, 4.96; N, 12.54; Cl, 7.93. Found: C, 51.02; H, 4.98; N, 12.46; Cl, 8.02.

Example 124

6-(3,4-Dimethylphenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.

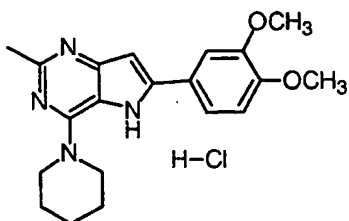
Using the method described in Example 30 by employing [1-(3,4-dimethylphenyl)vinyl]pyrrolidine (freshly prepared before use from 3,4-dimethyl acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl_4 (1.22 g, 6.07 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.30 g, 6.07 mmol), *N,N*-diisopropylethylamine (1.1 mL, 6.07 mmol), piperidine (1.0 mL, 9.7 mmol), NEt_3 (1.1 mL) and SnCl_2 (18 mL of a 2 M soln in DMF). In this example the reaction mixture was stirred at room temperature for 48 h after the addition of 2 M SnCl_2 . The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 605 mg (31%) of 6-(3,4-dimethylphenyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine as a beige colored solid. This material (605 mg, 1.88 mmol) was dissolved in 5:1 EtOAc/MeOH (35 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.90 mL, 1.90 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 518 mg (24%) of the title compound as a beige colored powder. Mp: 198-201 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.70 (br s, 6), 2.30 (s, 3), 2.33 (s, 3), 2.56 (s, 3), 4.05 (s, 4), 6.84 (s, 1), 7.32 (d, 1, $J = 7.9$), 7.70 (d, 1, $J = 7.8$), 7.74 (s, 1), 11.91 (s, 1), 14.38 (s, 1). MS m/z : 321 ($M+1$ for free base). Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_4 \cdot \text{HCl} \cdot 0.75\text{H}_2\text{O}$: C, 64.95; H, 7.17; N, 15.15; Cl, 9.47. Found: C, 65.13; H, 7.11; N, 14.98; Cl, 9.54.

**Example 125****6-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)-2H,3H-benzo[e]1,4-dioxane Hydrochloride Monohydrate.**

- 5 Using the method described in Example 30 by
 employing 6-(1-pyrrolidinylvinyl)-2H,3H-benzo[e]1,4-
 dioxane (freshly prepared before use from 1,4-
 benzodioxan-6-yl methyl ketone (Aldrich Chemical
 Company), pyrrolidine and TiCl_4 (1.75 g, 7.58 mmol), 2-
 10 methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b))
 (1.62 g, 7.58 mmol), *N,N*-diisopropylethylamine (1.3 mL,
 7.58 mmol), piperidine (1.2 mL, 12.2 mmol), NEt_3 (1.3
 mL) and SnCl_2 (23 mL of a 2 M soln in DMF). In this
 example the reaction mixture was stirred at room
 15 temperature for 48 h after the addition of 2 M SnCl_2 .
 The residue was purified by flash chromatography on
 silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 781
 mg (29%) of 6-(2-methyl-4-piperidylpyrrolo[4,5-d]
 pyrimidin-6-yl)-2H,3H-benzo[e]1,4-dioxane as a beige
 20 colored solid. This material (780 mg, 2.25 mmol) was
 dissolved in 5:1 EtOAc/MeOH (70 mL) and heated to
 boiling. To the hot solution was added 1 M ethereal
 HCl (2.30 mL, 2.30 mmol). The solution was left to
 cool to room temperature. The resulting crystals were
 25 collected by filtration, washed with EtOAc (2 x 10 mL),
 Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give
 690 mg (23%) of the title compound as a beige colored
 powder. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ
 1.70 (br s, 6), 2.56 (s, 3), 4.03 (s, 4), 4.32 (s, 4),
 30 6.81 (s, 1), 7.03 (d, 1, $J = 8.5$), 7.46 (dd, 1, $J =$
 2.2, 8.5), 7.55 (d, 1, $J = 2.1$), 11.81 (s, 1), 14.37

(s, 1). MS m/z : 351 ($M+1$ for free base). Anal. Calcd for $C_{20}H_{22}N_4O_2 \cdot HCl \cdot H_2O$: C, 59.32; H, 6.22; N, 13.84; Cl, 8.76. Found: C, 59.23; H, 6.28; N, 13.74; Cl, 8.65.

5

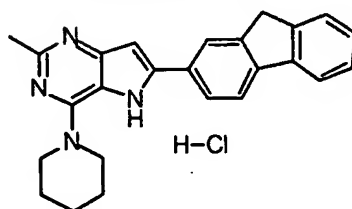
Example 126

1,2-Dimethoxy-4-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzene Hydrochloride Hydrate.

Using the method described in Example 30 by
10 employing 1,2-dimethoxy-4-(1-pyrrolidinylvinyl)benzene
(freshly prepared before use from 3,4-dimethoxy
acetophenone (Aldrich Chemical Company), pyrrolidine
and $TiCl_4$ (1.71 g, 7.34 mmol), 2-methyl-4,6-dichloro-5-
nitropyrimidine (Example 76(b)) (1.50 g, 7.34 mmol),
15 N,N -diisopropylethylamine (1.3 mL, 7.34 mmol),
piperidine (1.2 mL, 11.7 mmol), NEt_3 (1.3 mL) and $SnCl_2$
(22 mL of a 2 M soln in DMF). In this example the
reaction mixture was stirred at room temperature for 48
h after the addition of 2 M $SnCl_2$. The residue was
20 purified by flash chromatography on silica gel with
95:5 $CHCl_3/MeOH$ as eluant to give 1.51 g (59%) of 1,2-
dimethoxy-4-(2-methyl-4-piperidylpyrrolo[4,5-d]
pyrimidin-6-yl)benzene as a brown colored solid. This
material (1.51 g, 4.25 mmol) was dissolved in 5:1
25 $EtOAc/MeOH$ (90 mL) and heated to boiling. To the hot
solution was added 1 M ethereal HCl (4.30 mL, 4.30
mmol). The solution was left to cool to room
temperature. The resulting crystals were collected by
filtration, washed with $EtOAc$ (2 x 10 mL), Et_2O (3 x 15
30 mL) and dried under vacuum at 60 °C to give 0.95 g
(34%) of the title compound as a white colored solid.

221

Mp: 268-270 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.71 (br s, 6), 2.57 (s, 3), 3.83 (s, 3), 3.89 (s, 3), 4.05 (s, 4), 6.85 (s, 1), 7.13 (d, 1, *J* = 8.4), 7.50-7.54 (m, 2), 11.90 (s, 1), 14.30 (s, 1). MS *m/z*: 353 (*M*+1 for free base). Anal. Calcd for C₂₀H₂₄N₄O₂•HCl•1.25H₂O: C, 58.33; H, 6.68; N, 13.61; Cl, 8.51. Found: C, 58.31; H, 6.70; N, 13.54; Cl, 8.49.

Example 127

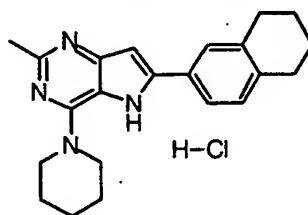
10

6-Fluoren-2-yl-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing (1-fluoren-2-ylvinyl)pyrrolidine (freshly prepared before use from 2-acetylfluorene (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.27 g, 4.86 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.01 g, 4.86 mmol), *N,N*-diisopropylethylamine (0.9 mL, 4.86 mmol), piperidine (0.8 mL, 7.8 mmol), NET₃ (1.0 mL) and SnCl₄ (15 mL of a 2 M soln in DMF). In this example the reaction mixture was stirred at room temperature for 48 h after the addition of 2 M SnCl₄. The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 325 mg (18%) of 6-fluoren-2-yl-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a beige colored solid. This material (321 mg, 0.86 mmol) was dissolved in 1:10 EtOAc/MeOH (60 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.90 mL, 0.90 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by

25
30

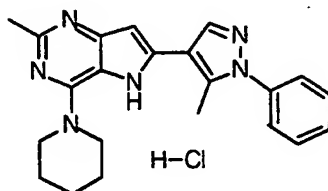
filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 138 mg (7%) of the title compound as a beige colored solid. Mp: >280 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.73 (br s, 6), 2.57 (s, 3), 4.05 (s, 2), 4.08 (br s, 4), 6.97 (s, 1), 7.39 (t, 1, *J* = 7.2), 7.44 (t, 1, *J* = 7.0), 7.66 (d, 1, *J* = 7.2), 8.02 (d, 2, *J* = 7.7), 8.10 (d, 1, *J* = 8.0), 8.21 (s, 1), 12.01 (s, 1), 14.27 (s, 1). MS *m/z*: 381 (M+1 for free base). Anal. Calcd for C₂₅H₂₄N₄•HCl•1.5H₂O: C, 67.58; H, 6.31; N, 12.61; Cl, 7.88. Found: C, 67.77; H, 6.25; N, 12.54; Cl, 8.06.

Example 128

2-Methyl-4-piperidyl-6-(2-5,6,7,8-tetrahydronaphthyl)pyrrolo[3,2-d]pyrimidine Hydrochloride Dihydrate.

Using the method described in Example 30 by employing ((1-(2-5,6,7,8-tetrahydronaphthyl)vinyl)pyrrolidine (freshly prepared before use from 6-acetyltetralin (Lancaster Chemical Company), pyrrolidine and TiCl₄ (1.37 g, 6.03 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.20 g, 6.03 mmol), *N,N*-diisopropylethylamine (1.0 mL, 6.03 mmol), piperidine (1.0 mL, 9.6 mmol), NEt₃ (1.0 mL) and SnCl₂ (18 mL of a 2 M soln in DMF). In this example the reaction mixture was stirred at room temperature for 48 h after the addition of 2 M SnCl₂. The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 692 mg (33%) of 2-methyl-4-piperidyl-6-(2-5,6,7,8-tetrahydronaphthyl)pyrrolo[3,2-d]pyrimidine as a white colored solid.

This material (692 mg, 2.00 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (2.00 mL, 2.00 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 563 mg (24%) of the title compound as a faint yellow colored solid. Mp: 175-177 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.71 (br s, 6), 1.78 (m, 4), 2.57 (s, 3), 2.82 (d, 4, J = 16.0), 4.06 (br s, 4), 6.93 (s, 1), 7.23 (d, 1, J = 8.6), 7.65-7.67 (m, 2), 11.92 (s, 1), 14.45 (s, 1). MS m/z: 347 (M+1 for free base). Anal. Calcd for C₂₂H₂₆N₄•HCl•2.0H₂O: C, 63.02; H, 7.40; N, 13.37; Cl, 8.35. Found: C, 63.18; H, 7.43; N, 13.41; Cl, 8.62.



Example 129

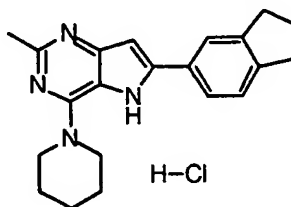
2-Methyl-6-(5-methyl-1-phenylpyrazol-4-yl)-4-piperidyl pyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing 5-methyl-1-phenyl-4-(1-pyrrolidinylvinyl) pyrazole (freshly prepared before use from 4-acetyl-5-methyl-1-phenylpyrazole (Maybridge Chemical Company), pyrrolidine and TiCl₄ (1.30 g, 5.14 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.00 g, 5.14 mmol), *N,N*-diisopropylethylamine (1.0 mL, 5.14 mmol), piperidine (0.8 mL, 8.2 mmol), NEt₃ (1.0 mL) and SnCl₂ (15 mL of a 2 M soln in DMF). In this example the reaction mixture was stirred at room temperature for 48 h after the addition of 2 M SnCl₂. The residue

was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 701 mg (37%) of 2-methyl-6-(5-methyl-1-phenylpyrazol-4-yl)-4-piperidyl pyrrolo[3,2-d]pyrimidine as a cream colored solid.

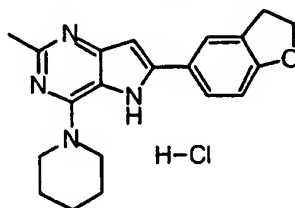
5 This material (700 mg, 1.89 mmol) was dissolved in 4:1 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.90 mL, 1.90 mmol). The solution was left to cool to room temperature. The resulting crystals were collected by
10 filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 637 mg (31%) of the title compound as white colored long needles. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.71 (br s, 6), 2.48 (s, 3), 2.57 (s, 3), 4.04 (br s, 4), 6.57 (s, 1), 7.48-7.62 (m, 5), 8.16 (s, 1), 11.89
15 (s, 1), 14.13 (s, 1). MS m/z: 373 (M+1 for free base). Anal. Calcd for C₂₂H₂₄N₆•HCl•0.25H₂O: C, 63.86; H, 6.17; N, 20.32; Cl, 8.47. Found: C, 64.11; H, 6.18; N, 20.43; Cl, 8.57.

20

Example 130**6-Indan-5-yl-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.**

25 Using the method described in Example 30 by employing (1-indan-5-ylvinyl)pyrrolidine (freshly prepared before use from 5-acetylidane (Avocado Chemical Company), pyrrolidine and TiCl₄ (1.35 g, 6.34 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example
30 76(b)) (1.35 g, 6.34 mmol), *N,N*-diisopropylethylamine (1.1 mL, 6.34 mmol), piperidine (1.0 mL, 10.1 mmol),

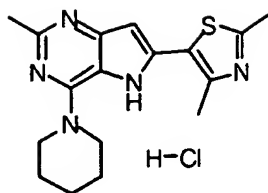
NEt₃ (1.1 mL) and SnCl₂ (19 mL of a 2 M soln in DMF). In this example the 2 M SnCl₂ solution was added to the reaction mixture at 140 °C. Heating was then discontinued and the mixture was allowed to cool to room temperature. The mixture was stirred at room temperature for an additional 48 h. The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 913 mg (43%) of 6-indan-5-yl-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine as a beige colored solid. This compound (909 mg, 2.75 mmol) was dissolved in 5:1 EtOAc/MeOH (50 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (2.80 mL, 2.80 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 601 mg (26%) of the title compound as a beige colored solid. Mp: 164-167 °C. ¹H NMR (DMSO-*d*₆; 500 MHz): δ 1.71 (br s, 6), 2.07 (quintet, 2, *J* = 7.4), 2.56 (s, 3), 2.94 (quintet, 4, *J* = 7.4), 4.05 (br s, 4), 6.83 (s, 1), 7.41 (d, 1, *J* = 7.8), 7.72 (d, 1, *J* = 8.0), 7.81 (s, 1), 11.88 (s, 1), 14.31 (s, 1). MS *m/z*: 333 (M+1 for free base). Anal. Calcd for C₂₁H₂₄N₄•HCl•H₂O: C, 65.18; H, 7.03; N, 14.48; Cl, 9.16. Found: C, 64.91; H, 6.96; N, 14.35; Cl, 9.22.

Example 131

5-[2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]-
2,3-dihydrobenzo[*b*]furan Hydrochloride Hydrate.

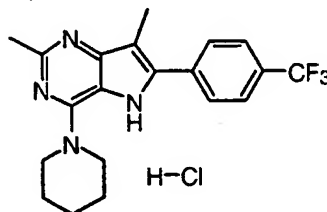
Using the method described in Example 30 by employing 5-(1-pyrrolidinylvinyl)-2,3-dihydrobenzo[b]furan (freshly prepared before use from 5-acetyl-2,3-dihydrobenzo[b]furan (Avocado Chemical Company), pyrrolidine and TiCl_4 (1.20 g, 5.58 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.20 g, 5.58 mmol), *N,N*-diisopropylethylamine (1.0 mL, 5.58 mmol), piperidine (0.9 mL, 8.9 mmol), NEt_3 (1.1 mL) and SnCl_2 (17 mL of a 2 M soln in DMF). In this example the 2 M SnCl_2 solution was added to the reaction mixture at 140 °C. Heating was then discontinued and the mixture was allowed to cool to room temperature. The mixture was stirred at room temperature for an additional 48 h. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 686 mg (37%) of 5-[2-methyl-4-piperidyl pyrrolo[4,5-d]pyrimidin-6-yl]-2,3-dihydrobenzo[b]furan as a beige colored solid. This compound (686 mg, 2.05 mmol) was dissolved in 3:1 EtOAc/MeOH (50 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (2.10 mL, 2.10 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 591 mg (29%) of the title compound as a beige colored powder. Mp: 170-172 °C. ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.69 (br s, 6), 2.56 (s, 3), 3.29 (t, 2, $J = 8.7$), 4.04 (br t, 4, $J = 5.4$), 4.63 (t, 2, $J = 8.7$), 6.76 (s, 1), 6.94 (d, 1, $J = 8.3$), 7.74 (d, 1, $J = 8.3$), 7.85 (s, 1), 11.78 (s, 1), 14.21 (s, 1). MS m/z : 335 ($M+1$ for free base). Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O} \cdot \text{HCl} \cdot 1.25\text{H}_2\text{O}$: C, 61.01; H, 6.48; N, 14.23; Cl, 8.90. Found: C, 61.17; H, 6.64; N, 14.19; Cl, 8.89.

227

**Example 132****2,4-Dimethyl-5-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-1,3-thiazole Hydrochloride Hydrate.**

5 Using the method described in Example 30 by
employing 2,4-dimethyl-5-(1-pyrrolidinylvinyl)-1,3-
thiazole (freshly prepared before use from 5-acetyl-
2,4-dimethylthiazole (Acros Chemical Company),
pyrrolidine and TiCl_4 (1.35 g, 6.45 mmol), 2-methyl-
10 4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.32 g,
6.45 mmol), *N,N*-diisopropylethylamine (1.1 mL, 6.45
mmol), piperidine (1.0 mL, 10.3 mmol), NEt_3 (1.1 mL)
and SnCl_2 (19 mL of a 2 M soln in DMF). In this
15 example the 2 M SnCl_2 solution was added to the
reaction mixture at 140 °C. Heating was then
discontinued and the mixture was allowed to cool to
room temperature. The mixture was stirred at room
temperature for an additional 48 h. The residue was
purified by flash chromatography on silica gel with
20 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 356 mg (17%) of 2,4-
dimethyl-5-[2-methyl-4-piperidylpyrrolo[4,5-d]
pyrimidin-6-yl]-1,3-thiazole as a beige colored solid.
This compound (356 mg, 1.10 mmol) was dissolved in 4:1
 EtOAc/MeOH (20 mL) and heated to boiling. To the hot
25 solution was added 1 M ethereal HCl (1.10 mL, 1.10
mmol). The solution was allowed to cool to room
temperature. The resulting solid was collected by
filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15
mL) and dried under vacuum at 60 °C to give 332 mg
30 (16%) of the title compound as a cream colored solid.
Mp: 272-273.5 °C. ^1H NMR ($\text{DMSO}-d_6$; 500 MHz): δ 1.63

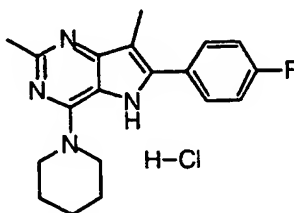
(br d, 6, $J = 5.4$), 2.37 (s, 3), 2.50 (s, 3), 2.62 (s, 3), 3.96 (br t, 4, $J = 4.7$), 6.56 (s, 1), 12.22 (s, 1), 14.44 (s, 1). MS m/z : 328 ($M+1$ for free base). Anal. Calcd for $C_{17}H_{21}N_5S \cdot 1.2HCl \cdot 1.5H_2O$: C, 51.27; H, 6.38; N, 17.59; Cl, 1041. Found: C, 51.59; H, 6.35; N, 17.48; Cl, 10.68.

Example 133

10 2,7-Dimethyl-4-piperidyl-6-[(4-trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidine Hydrochloride.

Using the method described in Example 30 by employing [(1-(4-trifluoromethyl)phenyl)prop-1-enyl]pyrrolidine (freshly prepared before use from 4'-trifluoromethyl)propiophenone (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (1.82 g, 7.13 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.51 g, 7.13 mmol), *N,N*-diisopropylethylamine (1.1 mL, 7.13 mmol), piperidine (1.1 mL, 11.4 mmol), NEt_3 (1.1 mL) and $SnCl_4$ (21 mL of a 2 M soln in DMF). In this example the $SnCl_4$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$ /MeOH as eluant to give 382 mg (14%) of 2,7-dimethyl-4-piperidyl-6-[(4-trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidine as a beige colored solid. This compound (382 mg, 1.02 mmol) was dissolved in 10:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was

added 1 M ethereal HCl (1.00 mL, 1.00 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 199 mg (7%) of the title compound as a beige colored powder. Mp: >280 °C. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.69 (br s, 6), 2.35 (s, 3), 2.63 (s, 3), 4.04 (br s, 4), 7.91 (d, 2, J = 8.1), 7.96 (d, 2, J = 8.2), 12.03 (s, 1), 13.97 (s, 1). MS m/z: 375 (M+1 for free base). Anal. Calcd for C₂₀H₂₁F₃N₄•HCl: C, 58.47; H, 5.40; N, 13.64; Cl, 8.63. Found: C, 58.23; H, 5.38; N, 13.53; Cl, 8.76.



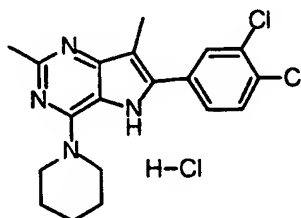
Example 134

6-(4-Fluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing [(1-(4-fluorophenyl)prop-1-enyl]pyrrolidine (freshly prepared before use from 4'-fluoropropiophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.65 g, 8.04 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.70 g, 8.04 mmol), N,N-diisopropylethylamine (1.4 mL, 8.04 mmol), piperidine (1.3 mL, 12.9 mmol), NEt₃ (1.4 mL) and SnCl₂ (24 mL of a 2 M soln in DMF). In this example the SnCl₂ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with

230

95:5 CHCl₃/MeOH as eluant to give 608 mg (23%) of 6-(4-fluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a brown colored gummy solid. This compound (601 mg, 1.85 mmol) was dissolved in 5:1
5 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.90 mL, 1.90 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15
10 mL) and dried under vacuum at 60 °C to give 285 mg (10%) of the title compound as a beige colored powder. Mp: >280 °C. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.68 (br s, 6), 2.32 (s, 3), 2.63 (s, 3), 4.04 (br t, 4, J = 5.1), 7.43 (t, 2, J = 8.7), 7.72 (dd, 2, J = 7.8, 8.1), 11.93
15 (s, 1), 14.10 (s, 1). MS m/z: 325 (M+1 for free base). Anal. Calcd for C₁₉H₂₁FN₄•HCl•0.3H₂O: C, 62.30; H, 6.22; N, 15.30; Cl, 9.68. Found: C, 62.14; H, 6.11; N, 15.24; Cl, 9.66.



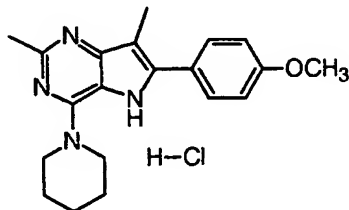
20

Example 135**6-(3,4-Dichlorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

Using the method described in Example 30 by
25 employing [(1-(3,4-dichlorophenyl)prop-1-enyl]pyrrolidine (freshly prepared before use from 3',4'-dichloropropiophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.64 g, 6.40 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.30 g,
30 6.40 mmol), N,N-diisopropylethylamine (1.1 mL, 6.40 mmol), piperidine (1.0 mL, 10.2 mmol), NEt₃ (1.1 mL)

and SnCl_2 (19 mL of a 2 M soln in DMF). In this example the SnCl_2 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 511 mg (21%) of 6-(3,4-dichlorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a brown colored oil. This compound (511 mg, 1.38 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.40 mL, 1.40 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 90 mg (3%) of the title compound as beige colored needles. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.64 (br s, 6), 2.27 (s, 3), 2.56 (s, 3), 3.98 (br t, 4, $J = 5.4$), 7.60 (dd, 1, $J = 2.0, 8.4$), 7.78 (d, 1, $J = 8.4$), 7.91 (d, 1, $J = 2.0$), 11.93 (s, 1), 13.97 (s, 1). MS m/z : 375 ($M+1$ for free base). Anal. Calcd for $\text{C}_{19}\text{H}_{20}\text{Cl}_2\text{N}_4 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 54.23; H, 5.27; N, 13.32; Cl, 25.28. Found: C, 54.35; H, 5.23; N, 13.29; Cl, 25.54.

Example 136

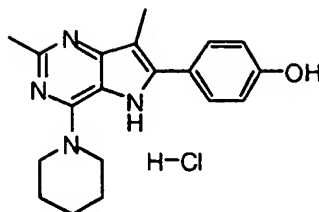


1-[2,7-Dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-4-methoxybenzene Hydrochloride.

Using the method described in Example 30 by employing 4-(1-pyrrolidinyprop-1-enyl)-1-methoxy

benzene (freshly prepared before use from 4'-methoxy propiophenone (Aldrich Chemical Company), pyrrolidine and TiCl_4 (1.77 g, 8.16 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.70 g, 8.20 mmol),
5 *N,N*-diisopropylethylamine (1.4 mL, 8.20 mmol), piperidine (1.3 mL, 13.1 mmol), NEt_3 (1.4 mL) and SnCl_2 (25 mL of a 2 M soln in DMF). In this example the SnCl_2 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional
10 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 894 mg (33%) of 1-[2,7-dimethyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]-
15 4-methoxybenzene as a brown colored foam. This compound (440 mg, 1.31 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.30 mL, 1.30 mmol). The solution was allowed to cool to room
20 temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 202 mg (14%) of the title compound as a beige colored sandy solid. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.62
25 (br s, 6), 2.24 (s, 3), 2.55 (s, 3), 3.94 (br s, 4), 7.08 (d, 2, $J = 8.7$), 7.55 (d, 2, $J = 8.7$), 11.76 (s, 1), 13.77 (s, 1). MS m/z : 337 ($M+1$ for free base).
Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{N}_4\text{O}\cdot\text{HCl}$: C, 64.42; H, 6.76; N, 15.03; Cl, 9.51. Found: C, 64.40; H, 6.68; N, 15.03;
30 Cl, 9.60.

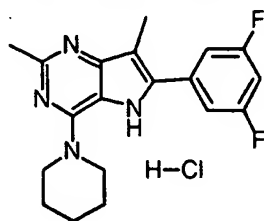
233

**Example 137****4-[2,7-Dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]phenol Hydrochloride Hydrate.**

- 5 To a -78 °C solution of 1-[2,7-dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-4-methoxybenzene (Example 136) (0.45 g, 1.34 mmol) in CH₂Cl₂ (20 mL) under a N₂ atmosphere was added 1 M BBr₃ (2.6 mL, 2.60 mmol). The reaction mixture was allowed to warm to
- 10 room temperature. The mixture was stirred at room temperature for an additional 20 h. The reaction mixture was then poured onto ice-water (200 mL) and the pH of the aqueous solution was adjusted to pH 9 with the addition of NEt₃ (2 mL). The resulting mixture was
- 15 stirred at room temperature for 2 h. The mixture was transferred to a separatory funnel. The organic solution was separated, washed with H₂O (100 mL), saturated NaCl (100 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to afford 272 mg
- 20 (64%) of 4-[2,7-dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]phenol as a beige colored solid. This compound (272 mg, 0.80 mmol) was dissolved in 4:2:1 EtOAc/MeOH/CH₂Cl₂ (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.80 mL, 0.80
- 25 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 107 mg (23%) of the title compound as brown colored crystals.
- 30 Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.61 (br s, 6), 2.24 (s, 3), 2.54 (s, 3), 3.93 (br s, 4), 6.91 (d,

234

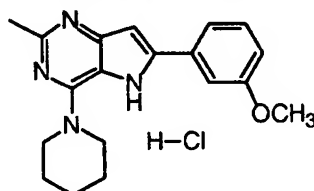
2, $J = 8.1$), 7.43 (d, 2, $J = 8.4$), 9.96 (s, 1), 11.70 (s, 1), 13.94 (s, 1). MS m/z : 323 ($M+1$ for free base). Anal. Calcd for $C_{19}H_{22}N_4O \cdot HCl \cdot 0.75H_2O$: C, 61.28; H, 6.63; N, 15.05; Cl, 9.52. Found: C, 61.32; H, 6.62; N, 14.96; Cl, 9.45.

Example 138

6-(3,5-Difluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo
10 **[3,2-d]pyrimidine Hydrochloride Hydrate.**

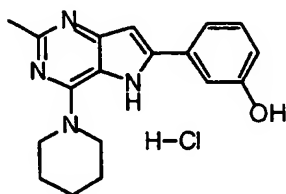
Using the method described in Example 30 by employing (1-(3,5-difluorophenyl)prop-1-enyl)pyrrolidine (freshly prepared before use from 3,5-difluoropropiophenone (Lancaster Chemical Company), pyrrolidine and $TiCl_4$ (2.29 g, 10.3 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.10 g, 10.3 mmol), *N,N*-diisopropylethylamine (1.8 mL, 10.3 mmol), piperidine (1.6 mL, 16.4 mmol), NEt_3 (1.6 mL) and $SnCl_2$ (31 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3$ /MeOH as eluant to give 605 mg (17%) of 6-(3,5-difluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a beige colored foam. This compound (600 mg, 1.75 mmol) was dissolved in 10:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.80 mL, 1.80 mmol). The solution was allowed to

cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 291 mg (7%) of the title compound as a beige colored solid. Mp: 242-245 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.52 (br s, 6), 2.28 (s, 3), 2.55 (s, 3), 3.97 (br s, 4), 7.36-7.41 (m, 3), 11.89 (s, 1), 13.82 (s, 1). MS m/z: 343 (M+1 for free base). Anal. Calcd for C₁₉H₂₀F₂N₄•HCl•0.5H₂O: C, 58.83; H, 5.72; N, 14.45; Cl, 9.24. Found: C, 58.86; H, 5.72; N, 14.50; Cl, 9.29.

Example 139**1-[2,7-Dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-3-methoxybenzene Hydrochloride Hydrate.**

Using the method described in Example 30 by employing 1-methoxy-3-(1-pyrrolidinylvinyl)benzene (freshly prepared before use from 3-methoxyacetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (2.49 g, 12.3 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.52 g, 12.3 mmol), *N,N*-diisopropylethylamine (2.1 mL, 12.3 mmol), piperidine (1.9 mL, 19.7 mmol), NEt₃ (2.0 mL) and SnCl₂ (37 mL of a 2 M soln in DMF). In this example the SnCl₂ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 1.35 g (34%) of 1-[2,7-dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-

- 3-methoxybenzene as a beige colored solid. This compound (463 mg, 1.43 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.50 mL, 1.50 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 485 mg (32%) of the title compound as a white colored solid.
- 10 Mp: 241-243 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.64 (br s, 6), 2.50 (s, 3), 3.79 (s, 3), 3.98 (br s, 4), 6.84 (s, 1), 7.03 (dd, 1, J = 1.0, 8.3), 7.38 (t, 1, J = 3.9), 7.44-7.46 (m, 2), 11.91 (s, 1), 14.36 (s, 1). MS m/z: 323 (M+1 for free base). Anal. Calcd for
- 15 C₁₉H₂₂N₄O•HCl•0.5H₂O: C, 62.03; H, 6.58; N, 15.23; Cl, 9.64. Found: C, 62.08; H, 6.56; N, 15.17; Cl, 9.75.

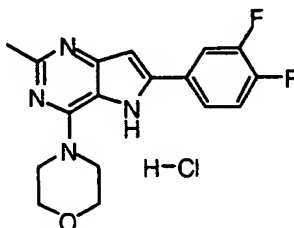


Example 140

- 20 **3-[2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]phenol Hydrochloride Hydrate.**

- To a -78 °C solution of 1-[2,7-dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-3-methoxybenzene (Example 139) (0.89 g, 2.76 mmol) in CH₂Cl₂ (40 mL) under a N₂ atmosphere was added 1 M BBr₃ (5.50 mL, 5.50 mmol). The reaction mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for an additional 20 h. The reaction mixture was then poured onto ice-water (200 mL) and the
- 30 pH of the aqueous solution was adjusted to pH 9 with the addition of NEt₃ (2 mL). CH₂Cl₂ (60 mL) added and

the resulting mixture was stirred at room temperature for 2 h. The mixture was transferred to a separatory funnel. The organic solution was separated, washed with H₂O (100 mL), saturated NaCl (100 mL), dried (MgSO₄), filtered and concentrated under reduced pressure to afford 0.90 g (100%) of 3-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]phenol as a beige colored solid. This compound (0.90 mg, 5.00 mmol) was dissolved in 5:1:1 EtOAc/MeOH/CH₂Cl₂ (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (5.00 mL, 5.00 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 525 mg (55%) of the title compound as white colored crystals. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.63 (br s, 6), 2.48 (s, 3), 3.97 (br s, 4), 6.73 (s, 1), 6.84-6.87 (m, 1), 7.24 (br s, 1), 7.27-7.28 (m, 2), 9.75 (s, 1), 11.61 (s, 1), 13.87 (s, 1). MS m/z: 309 (M+1 for free base). Anal. Calcd for C₁₈H₂₀N₄O•HCl•1.3H₂O: C, 58.70; H, 6.46; N, 15.22; Cl, 9.63. Found: C, 59.09; H, 6.11; N, 14.91; Cl, 9.30.

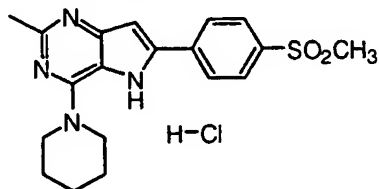
Example 141

4-[6-(3,4-Difluorophenyl)-2-methylpyrrolo[2,3-e]pyrimidin-4-yl]morpholine Hydrochloride.

Using the method described in Example 30 by employing (1-(3,4-difluorophenyl)vinyl)pyrrolidine (freshly prepared before use from 3,4-difluoro acetophenone (Aldrich Chemical Company), pyrrolidine

and TiCl_4 (2.04 g, 9.76 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.02 g, 9.76 mmol), *N,N*-diisopropylethylamine (1.7 mL, 9.76 mmol), morpholine (1.4 mL, 15.6 mmol), NEt_3 (1.5 mL) and SnCl_2 (29 mL of a 2 M soln in DMF). In this example the SnCl_2 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 0.78 g (24%) of 4-[6-(3,4-difluorophenyl)-2-methylpyrrolo[2,3-*e*]pyrimidin-4-yl]morpholine as a beige colored solid. This compound (780 mg, 3.00 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (3.00 mL, 3.00 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 670 mg (15%) of the title compound as pale yellow colored crystals. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 2.37 (s, 3), 3.59 (br s, 4), 3.89 (br s, 4), 6.78 (s, 1), 7.40 (q, 1, $J = 8.8$), 7.68 (br s, 1), 8.00 (t, 1, $J = 9.8$), 11.94 (s, 1), 14.48 (s, 1). MS m/z : 331 ($M+1$ for free base). Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{F}_2\text{N}_4\text{O} \cdot \text{HCl}$: C, 55.66; H, 4.67; N, 15.28; Cl, 9.66. Found: C, 55.57; H, 4.77; N, 15.15; Cl, 9.61.

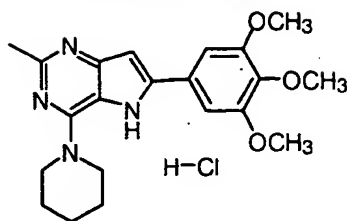
30

Example 142

1-[2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-4-(methylsulfonyl)benzene Hydrochloride Monohydrate.

Using the method described in Example 30 by employing 1-(methylsulfonyl)-4-(1-pyrrolidinylvinyl) benzene (freshly prepared before use from 3-methyl sulfonylacetophenone (Acros Chemical Company), pyrrolidine and TiCl_4 (2.01 g, 8.00 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.71 g, 8.00 mmol), *N,N*-diisopropylethylamine (1.4 mL, 8.0 mmol), piperidine (1.3 mL, 12.8 mmol), NEt_3 (1.4 mL) and SnCl_4 (24 mL of a 2 M soln in DMF). In this example the SnCl_4 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 1.10 g (37%) of 1-[2-methyl-4-piperidyl pyrrolo[4,5-d]pyrimidin-6-yl]-4-(methylsulfonyl)benzene as a beige colored solid. This compound (1.10 g, 2.97 mmol) was dissolved in 4:1 EtOAc/MeOH (50 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (3.00 mL, 3.00 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 1.05 g (32%) of the title compound as a beige colored solid. Mp: 279-281 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.65 (br s, 6), 2.51 (s, 3), 3.23 (s, 3), 4.01 (br s, 4), 7.02 (s, 1), 7.93, 8.27 (AB q, 4, J = 8.3, 8.3), 12.14 (s, 1), 14.38 (s, 1). MS m/z : 371 ($M+1$ for free base). Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_2\text{S}\cdot\text{HCl}\cdot\text{H}_2\text{O}$: C, 53.70; H, 5.93; N, 13.19; Cl, 8.34. Found: C, 53.82; H, 5.94; N, 13.08; Cl, 8.49.

Example 143

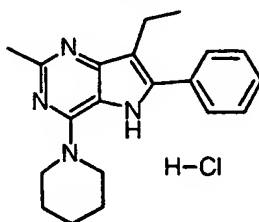


1,2,3-Trimethoxy-5-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzene Hydrochloride.

5 Using the method described in Example 30 by employing 1,2,3-trimethoxy-5-(1-pyrrolidinylvinyl) benzene (freshly prepared before use from 3,4,5-trimethoxyacetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (1.70 g, 6.46 mmol), 2-methyl-10 4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.35 g, 6.46 mmol), *N,N*-diisopropylethylamine (1.1 mL, 6.46 mmol), piperidine (1.0 mL, 10.3 mmol), NEt₃ (1.1 mL) and SnCl₄ (19 mL of a 2 M soln in DMF). In this example the SnCl₄ solution was added to the reaction 15 mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as 20 eluant to give 0.85 g (35%) of 1,2,3-trimethoxy-5-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzene as a beige colored solid. This compound (466 mg, 1.20 mmol) was dissolved in 1:3 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M 25 ethereal HCl (1.20 mL, 1.20 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 409 mg (29%) of the title 30 compound as white colored crystals. Mp: 275-277 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.64 (br s, 6), 2.52 (s, 3),

241

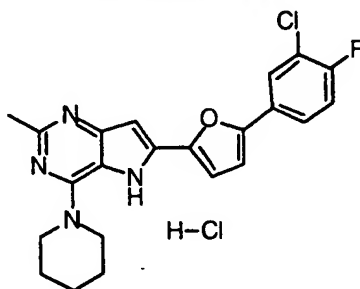
3.66 (s, 3), 3.39 (s, 6), 3.99 (br t, 4, $J = 5.2$), 6.85 (s, 1), 7.75 (s, 2), 11.94 (s, 1), 14.28 (s, 1). MS m/z : 381 ($M+1$ for free base). Anal. Calcd for $C_{21}H_{26}N_4O_3 \cdot HCl$: C, 60.21; H, 6.50; N, 13.37; Cl, 8.46.
5 Found: C, 60.24; H, 6.53; N, 13.37; Cl, 8.57.

Example 144

10 **7-Ethyl-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

Using the method described in Example 30 by employing (1-phenylbut-1-enyl)pyrrolidine (freshly prepared before use from butyrophenone (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (1.63 g, 8.11 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 15 76(b)) (1.60 g, 8.11 mmol), *N,N*-diisopropylethylamine (1.4 mL, 8.11 mmol), piperidine (1.3 mL, 13.0 mmol), NEt_3 (1.3 mL) and $SnCl_2$ (24 mL of a 2 M soln in DMF). In this example the $SnCl_2$ solution was added to the
20 reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 100% EtOAc as eluant
25 to give 0.42 g (16%) of 7-ethyl-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a beige colored solid. This compound (411 mg, 1.31 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to boiling. To
30 the hot solution was added 1 M ethereal HCl (1.30 mL, 1.30 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by

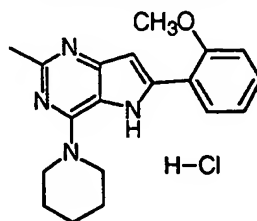
filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 34 mg (1%) of the title compound as a white colored solid. Mp: 261-263 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.05 (t, 3, *J* = 7.5), 1.63 (br s, 6), 2.56 (s, 3), 2.69 (q, 2, *J* = 7.2), 3.95 (br s, 4), 7.46-8.02 (m, 5), 11.90 (s, 1), 13.86 (s, 1). MS *m/z*: 321 (M+1 for free base). Anal. Calcd for C₂₀H₂₄N₄•HCl•0.7H₂O: C, 65.01; H, 7.20; N, 15.17; Cl, 9.59. Found: C, 65.09; H, 6.90; N, 14.98; Cl, 9.85.

Example 145

**5-(3-Chloro-4-fluorophenyl)-2-[2-methyl-4-piperidyl
pyrrolo[4,5-d]pyrimidin-6-yl]furan Hydrochloride
Hydrate.**

Using the method described in Example 30 by employing 5-(3-chloro-4-fluorophenyl)-2-(1-pyrrolidinyl vinyl)furan (freshly prepared before use from 1-[5-(3-chloro-4-fluorophenyl)-2-furyl]ethan-1-one (Maybridge Chemical Company), pyrrolidine and TiCl₄ (1.65 g, 5.67 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.20 g, 5.67 mmol), *N,N*-diisopropylethylamine (1.0 mL, 5.67 mmol), piperidine (0.9 mL, 9.1 mmol), NEt₃ (1.0 mL) and SnCl₄ (17 mL of a 2 M soln in DMF). In this example the SnCl₄ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to

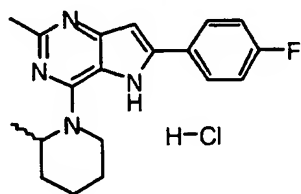
room temperature. The residue was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 0.61 g (26%) of 5-(3-chloro-4-fluorophenyl)-2-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]furan as a beige colored solid. This compound (609 mg, 1.50 mmol) was dissolved in 10:1 EtOAc/MeOH (25 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.50 mL, 1.50 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 385 mg (15%) of the title compound as tan colored small needles. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.65 (br s, 6), 2.51 (s, 3), 4.00 (br s, 4), 6.89 (s, 1), 7.26 (d, 1, J = 3.7), 7.47 (d, 1, J = 3.7), 7.50 (t, 1, J = 9.0), 7.85-7.89 (m, 1), 8.10 (dd, 1, J = 2.1, 7.1), 12.19 (s, 1), 14.31 (s, 1). MS m/z: 411 (M+1 for free base). Anal. Calcd for C₂₂H₂₀ClFN₄O•HCl•1.5H₂O: C, 55.70; H, 5.10; N, 11.81; Cl, 14.95. Found: C, 55.80; H, 5.10; N, 11.72; Cl, 15.06.

Example 146**2-Methoxy-1-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzene Hydrochloride Monohydrate.**

Using the method described in Example 30 by employing 2-methoxy-1-(1-pyrrolidinylvinyl)furan (freshly prepared before use from 2'-methoxy acetophenone (Aldrich Chemical Company), pyrrolidine and TiCl₄ (2.14 g, 10.5 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.25 g, 10.5 mmol),

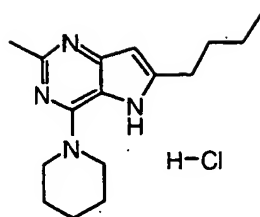
244

N,N-diisopropylethylamine (1.8 mL, 10.5 mmol),
piperidine (1.7 mL, 16.8 mmol), NEt₃ (1.8 mL) and SnCl₂
(32 mL of a 2 M soln in DMF). In this example the
SnCl₂ solution was added to the reaction mixture at 140
5 °C. The mixture was stirred at 140 °C for an additional
16 h then the heating was discontinued and the mixture
was allowed to cool to room temperature. The residue
was purified by flash chromatography on silica gel with
95:5 CHCl₃/MeOH as eluant to give 2.49 g (74%) of 2-
10 methoxy-1-[2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-
6-yl]benzene as a beige colored foam. This compound
(864 mg, 2.67 mmol) was dissolved in 10:1 EtOAc/MeOH
(60 mL) and heated to boiling. To the hot solution was
added 1 M ethereal HCl (2.70 mL, 2.70 mmol). The
15 solution was allowed to cool to room temperature. The
resulting crystals were collected by filtration, washed
with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried
under vacuum at 60 °C to give 654 mg (50%) of the title
compound as a pale yellow colored solid. Mp: 261-263
20 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.64 (br s, 6), 2.51
(s, 3), 3.83 (s, 3), 3.97 (br s, 4), 6.72 (s, 1), 7.07
(dt, 1, *J* = 0.7, 7.4), 7.18 (d, 1, *J* = 8.2), 7.44 (dt,
1, *J* = 1.7, 7.1), 7.67 (dd, 1, *J* = 1.3, 7.6), 11.74 (s,
1), 14.31 (s, 1). MS *m/z*: 411 (M+1 for free base).
25 Anal. Calcd for C₁₉H₂₂N₄O•HCl•H₂O: C, 60.55; H, 6.69; N,
14.87; Cl, 9.41. Found: C, 60.68; H, 6.78; N, 14.82;
Cl, 9.52.

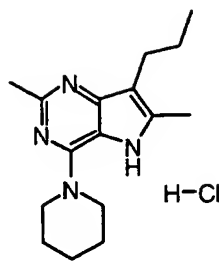
Example 147

**6-(4-Fluorophenyl)-2-methyl-4-(2-methylpiperidyl)
pyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.**

Using the method described in Example 30 by
employing [1-(4-fluorophenyl)vinyl]pyrrolidine (freshly
5 prepared before use from 4'-fluoroacetophenone (Aldrich
Chemical Company), pyrrolidine and TiCl_4 (2.17 g, 11.4
mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example
76(b)) (2.42 g, 11.4 mmol), *N,N*-diisopropylethylamine
(2.0 mL, 11.4 mmol), 2-methylpiperidine (2.1 mL, 18.2
10 mmol), NEt_3 (2.0 mL) and SnCl_2 (34 mL of a 2 M soln in
DMF). In this example the SnCl_2 solution was added to
the reaction mixture at 140 °C. The mixture was
stirred at 140 °C for an additional 16 h then the
heating was discontinued and the mixture was allowed to
15 cool to room temperature. The residue was purified by
flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$
as eluant to give 0.88 g (24%) of 6-(4-fluorophenyl)-2-
methyl-4-(2-methylpiperidyl)pyrrolo[3,2-d]pyrimidine as
a beige colored solid. This compound (882 mg, 2.71
20 mmol) was dissolved in 10:1 EtOAc/MeOH (50 mL) and
heated to boiling. To the hot solution was added 1 M
ethereal HCl (2.70 mL, 2.70 mmol). The solution was
allowed to cool to room temperature. The resulting
crystals were collected by filtration, washed with
25 EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under
vacuum at 60 °C to give 573 mg (14%) of the title
compound as a white colored solid. Mp: 274-276 °C. ^1H
NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.20 (d, 3, $J = 6.9$), 1.40-
1.73 (m, 6), 2.44 (s, 3), 3.35 (br s, 1), 4.48 (br s,
1), 5.13 (br s, 1), 6.75 (s, 1), 7.28 (t, 2, $J = 8.9$),
30 7.89 (dd, 2, $J = 5.4, 5.4$), 11.79 (s, 1), 14.04 (s, 1).
MS m/z : 325 ($M+1$ for free base). Anal. Calcd for
 $\text{C}_{19}\text{H}_{21}\text{FN}_4 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 60.23; H, 6.39; N, 14.79; Cl, 9.36.
Found: C, 60.60; H, 6.28; N, 14.90; Cl, 9.35.



Example 148



Example 149

Example 148 and Example 149

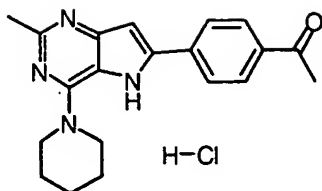
6-Butyl-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride and 2,6-Dimethyl-4-piperidyl-7-propylpyrrolo[3,2-d]pyrimidine Hydrochloride.

Using the method described in Example 30 by employing a mixture of [1-butylvinyl]pyrrolidine and [1-methylpent-1-enyl]pyrrolidine (freshly prepared before use from 2-hexanone (Aldrich Chemical Company), pyrrolidine and TiCl_4 (1.75 g, 11.4 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.42 g, 11.4 mmol), *N,N*-diisopropylethylamine (2.0 mL, 11.4 mmol), piperidine (1.8 mL, 18.2 mmol), NEt_3 (2.0 mL) and SnCl_4 (34 mL of a 2 M soln in DMF). In this example the SnCl_4 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 0.71 g (23%) of 6-butyl-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a beige colored foam and 326 mg (11%) of 2,6-dimethyl-4-piperidyl-7-propylpyrrolo[3,2-d]pyrimidine as a pale yellow colored solid.

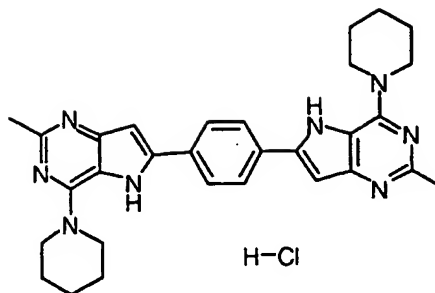
Example 148: 6-Butyl-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine (0.71 g, 2.61 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (2.60 mL, 2.60

mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 525 mg (15%) of Example 148 as white colored cube shaped crystals. Mp: 246-248 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.17 (t, 3, J = 7.4), 1.59 (quintet, 2, J = 7.3), 1.87-1.94 (m, 8), 2.77 (s, 3), 3.06 (t, 2, J = 7.8), 6.55 (s, 1), 12.08 (s, 1), 14.39 (s, 1). MS m/z: 273 (M+1 for free base). Anal. Calcd for C₁₆H₂₄N₄•HCl: C, 62.22; H, 8.16; N, 18.14; Cl, 11.48. Found: C, 62.31; H, 8.12; N, 18.18; Cl, 11.44.

Example 149: 2,6-Dimethyl-4-piperidyl-7-propyl pyrrolo[3,2-d]pyrimidine (326 mg, 1.20 mmol) was dissolved in 4:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.20 mL, 1.20 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 218 mg (6%) of Example 149 as beige colored cube needles. Mp: 265-267.5 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 0.83 (t, 3, J = 7.3), 1.40 (quintet, 2, J = 7.3), 1.58 (m, 6), 2.35 (s, 3), 2.43 (m, 1), 2.56 (t, 2, J = 7.1), 3.89 (s, 4), 11.79 (s, 1), 13.72 (s, 1). MS m/z: 273 (M+1 for free base). Anal. Calcd for C₁₆H₂₄N₄•HCl: C, 62.22; H, 8.16; N, 18.14; Cl, 11.48. Found: C, 61.98; H, 8.05; N, 18.02; Cl, 11.67.



Example 150



Example 151

Example 150 and Example 151

1-[4-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenyl]ethan-1-one Hydrochloride Hydrate and 2-Methyl-
 5 6-[4-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenyl]-4-piperidylpyrrolo[3,2-d]pyrimidine
 Hydrochloride hydrate.

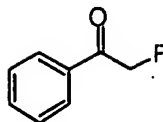
Using the method described in Example 30 by
 employing a mixture of 1-[4-(1-pyrrolidinylvinyl)
 10 phenyl]ethan-1-one and [1-(4-(1-pyrrolidinylvinyl)
 phenyl]vinyl]pyrrolidine (freshly prepared before use
 from 1,4-diacetylbenzene (Aldrich Chemical Company),
 pyrrolidine and TiCl_4 (1.93 g, 7.20 mmol), 2-methyl-
 4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.90 g,
 15 14.4 mmol), *N,N*-diisopropylethylamine (2.5 mL, 14.4
 mmol), piperidine (2.2 mL, 23.0 mmol), NEt_3 (2.3 mL)
 and SnCl_2 (43 mL of a 2 M soln in DMF). In this
 example the SnCl_2 solution was added to the reaction
 mixture at 140 °C. The mixture was stirred at 140 °C
 20 for an additional 16 h then the heating was
 discontinued and the mixture was allowed to cool to
 room temperature. The residue was purified by flash
 chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as
 eluant to give 188 g (8%) of 1-[4-(2-methyl-4-piperidyl
 25 pyrrolo[4,5-d]pyrimidin-6-yl)phenyl]ethan-1-one as a
 brown colored solid and 76 mg (2%) of 2-methyl-6-[4-(2-
 methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenyl]-

4-piperidylpyrrolo[3,2-d]pyrimidine as a yellow colored solid.

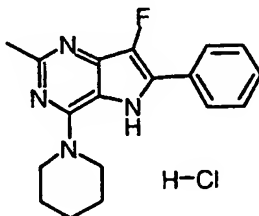
Example 150: 1-[4-(2-Methyl-4-piperidylpyrrolo [4,5-d]pyrimidin-6-yl)phenyl]ethan-1-one (188 mg, 0.60 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.60 mL, 0.60 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 104 mg (4%) of Example 150 as a yellow colored solid. Mp: 173.5-175 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.65 (br s, 6), 2.51 (s, 3), 2.57 (s, 3), 4.01 (br s, 4), 6.98 (s, 1), 8.05 (q, 4, J = 4.5), 12.02 (s, 1), 14.31 (s, 1). MS m/z: 335 (M+1 for free base). Anal. Calcd for C₂₀H₂₂N₄O•HCl•1.75H₂O: C, 56.69; H, 6.64; N, 13.93; Cl, 8.81. Found: C, 59.78; H, 6.53; N, 14.00; Cl, 8.91.

Example 151: 2-Methyl-6-[4-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenyl]-4-piperidylpyrrolo[3,2-d]pyrimidine (76 mg, 0.20 mmol) was dissolved in 5:2 EtOAc/MeOH (15 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.40 mL, 0.40 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 30 mg (1%) of Example 151 as a yellow colored powder. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.66 (br s, 12), 2.52 (s, 6), 4.02 (br s, 8), 6.96 (s, 2), 8.05 (s, 4), 12.01 (s, 2), 14.21 (s, 2). MS m/z: 507 (M+1 for free base). Anal. Calcd for C₃₀H₃₄N₈•2HCl•4H₂O: C, 55.29; H, 6.81; N, 17.20; Cl, 10.88. Found: C, 54.96; H, 6.62; N, 16.74; Cl, 11.00.

250

**Example 152****(a) 2-Fluoro-1-phenylethan-1-one.**

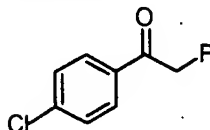
A mixture of 2-bromoacetophenone (Aldrich Chemical
5 Company) (5.42 g, 27.3 mmol), KF (6.32 g, 0.11 mol) and
18-crown-6 (3.61 g, 13.7 mmol) in CH₃CN (150 mL) was
heated at 90 °C for 16 h under a N₂ atmosphere. Heating
was discontinued and the mixture was allowed to cool to
room temperature. The mixture was diluted with H₂O
10 (300 mL) and EtOAc (400 mL) and transferred to a
separatory funnel. The organic solution was separated,
washed with H₂O (2 x 300 mL), saturated NaCl (300 mL),
dried (MgSO₄), filtered and concentrated under reduced
pressure. The resulting crude ketone (3.02 g) was used
15 without further purification (see Gregory et al. *J.*
Med. Chem. 1990, 33(9), 2569).

**(b) 7-Fluoro-2-methyl-6-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.**

20 To a room temperature solution of [2-fluoro-1-phenylvinyl]pyrrolidine (freshly prepared before use
from 2-fluoro-1-phenyl ethan-1-one (Example 152(a)),
pyrrolidine and TiCl₄ (see Example 30) (2.44 g, 12.7
mmol) in anhydrous toluene (15 mL) was added *N,N*-
diisopropylethylamine (Aldrich Chemical Company) (2.0
25 mL, 12.7 mmol) followed by 2-methyl-4,6-dichloro-5-
nitropyrimidine (Example 76(b)) (2.61 g, 12.7 mmol).
After stirring at room temperature for 2.5 h the
reaction mixture was filtered through a fritted funnel.

The residue was washed with hot toluene (2 x 30 mL) and the filtrate was concentrated under reduced pressure. The residue was dissolved with dioxane/toluene (20 mL:10 mL) and NEt_3 (Aldrich Chemical Company) (2.1 mL) and piperidine (Aldrich Chemical Company) (2.0 mL, 20.3 mmol) were added. The mixture was stirred at 80 °C for 2 h under a N_2 atmosphere. The SnCl_4 solution was added to the reaction mixture at 80 °C. The mixture was stirred at 80 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The reaction mixture was poured onto a mixture of NaOH (5g) and crushed ice (150 mL) and stirred for 1 h. The resulting slurry was filtered through a Celite® pad, the pad was rinsed with 10:1 EtOAc/MeOH (4 x 60 mL). The filtrate was transferred to a separatory funnel. The organic solution was separated, washed with H_2O (3 x 350 mL), saturated NaCl (300 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 0.51 g (13%) of 7-fluoro-2-methyl-6-piperidylpyrrolo[3,2-d]pyrimidine as a brown colored foam. This compound (0.51 g, 1.60 mmol) was dissolved in 10:1 EtOAc/MeOH (35 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.60 mL, 1.60 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 270 mg (6%) of the title compound as pale green colored needles. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.72 (br s, 6), 2.59 (s, 3), 4.07 (br s, 4), 7.53-7.57 (m, 1), 7.61 (t, 2, J = 7.7), 7.87 (d, 2, J = 7.5), 12.07 (s, 1), 14.56 (s, 1). MS m/z : 311 ($M+1$ for free base). Anal. Calcd for

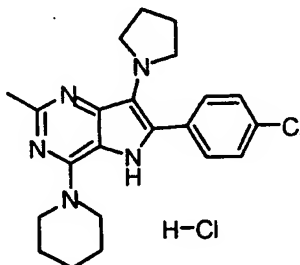
$C_{18}H_{19}FN_4 \cdot HCl$: C, 62.33; H, 5.81; N, 16.15; Cl, 10.22.
Found: C, 62.04; H, 5.95; N, 16.08; Cl, 10.02.

Example 153

5

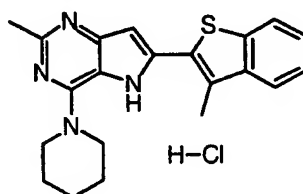
(a) 1-(4-Chlorophenyl)-2-fluoroethan-1-one.

Using the method described in Example 152(a) by employing 2-bromo-4'-chloroacetophenone (Aldrich Chemical Company) (4.06 g, 17.5 mmol), KF (4.1 g, 0.11 mol) and 18-crown-6 (3.61 g, 13.7 mmol). The resulting crude ketone was used without further purification.

**(b) 2-Methyl-6-phenyl-4-piperidyl-7-pyrrolidinyl pyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

Using the method described in Example 30 by employing [1-(4-chlorophenyl)-2-fluorovinyl]pyrrolidine (freshly prepared before use from 1-(4-chlorophenyl)-2-fluoroethan-1-one (Example 153(a)), pyrrolidine and $TiCl_4$ (see Example 30) (3.00 g, 13.3 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.80 g, 13.3 mmol), *N,N*-diisopropylethylamine (2.3 mL, 13.3 mmol), piperidine (2.1 mL, 21.3 mmol), NEt_3 (2.2 mL) and $SnCl_2$ (40 mL of a 2 M soln in DMF). In this example, the $SnCl_2$ solution was added to the reaction mixture at 140 °C. (Note: When both the piperidine displacement and the $SnCl_2$ reduction sequences are performed at 140 °C the pyrrolidine moiety is incorporated). The mixture was stirred at 140 °C for

an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 0.38 g (8%) of 2-methyl-6-phenyl-4-piperidyl-7-pyrrolidinylpyrrolo[3,2-d]pyrimidine as a brown colored solid. This compound (0.38 g, 1.00 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.00 mL, 1.00 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 162 mg (2%) of the title compound as a beige colored powder. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.49 (br s, 2), 1.54 (br s, 4), 1.88 (br s, 2), 2.01 (br s, 2), 2.59 (s, 3), 2.92 (br s, 4), 3.72 (br s, 2), 4.04 (br s, 2), 7.57 (d, 2, J = 8.5), 7.76 (d, 2, J = 8.4), 11.44 (s, 1), 13.13 (s, 1). MS m/z: 396 (M+1 for free base). Anal. Calcd for C₂₂H₂₆ClN₄•HCl•0.5H₂O: C, 59.86; H, 6.39; N, 15.87; Cl, 16.06. Found: C, 59.56; H, 6.36; N, 15.70; Cl, 15.95.

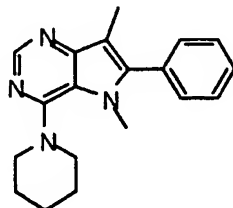
Example 154

3-Methyl-2-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzo[b]thiophene Hydrochloride Hydrate.

Using the method described in Example 30 by employing 3-methyl-2-(1-pyrrolidinylvinyl)benzo[b]thiophene (freshly prepared before use from 2-acetyl-3-methylthianaphthene (Avocado Chemical Company),

pyrrolidine and TiCl_4 (1.67 g, 6.88 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.43 g, 6.88 mmol), *N,N*-diisopropylethylamine (1.2 mL, 6.88 mmol), piperidine (1.1 mL, 11.0 mmol), NEt_3 (1.5 mL) and SnCl_2 (21 mL of a 2 M soln in DMF). In this example the SnCl_2 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 0.60 g (24%) of 3-methyl-2-[2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]benzo[*b*]thiophene as a beige colored solid. This compound (596 mg, 1.64 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.70 mL, 1.70 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 421 mg (16%) of the title compound as a pale yellow colored powder. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.65 (br s, 6), 2.46 (s, 3), 2.51 (s, 3), 3.98 (br s, 4), 6.67 (s, 1), 7.41–7.47 (m, 2), 7.87 (dd, 1, $J = 1.7, 6.2$), 7.99 (dd, 1, $J = 1.7, 6.4$), 12.43 (s, 1), 14.38 (s, 1). MS m/z : 363 ($M+1$ for free base). Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{S}\cdot\text{HCl}\cdot 0.4\text{H}_2\text{O}$: C, 62.10; H, 5.91; N, 13.80; Cl, 8.73. Found: C, 62.04; H, 5.92; N, 13.80; Cl, 8.83.

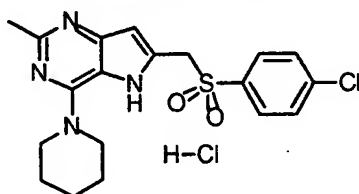
30



Example 155**5,7-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine.**

To a 0 °C solution of 7-methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 89) (177.3 mg, 0.61 mmol) in THF (10 mL) under a nitrogen atmosphere was added LiHMDS (1.0 M soln from Aldrich Chemical Company) (1.3 mL, 1.27 mmol). This mixture was stirred at 0 °C for 0.5 h then CH₃I (Aldrich Chemical Company) (41 mL, 0.67 mmol) was added. The 0 °C bath was removed and the solution stirred at room temperature for 2.5 h. The reaction mixture was poured into a separatory funnel containing EtOAc (35 mL) and H₂O (50 mL). The organic solution was collected washed with H₂O (3 x 40 mL), saturated NaCl (70 mL), dried (MgSO₄), filtered and concentrated under reduced pressure. The residue was purified via flash chromatography on silica gel 95:5 CHCl₃/MeOH as eluant to give 164 mg (86%) of the title compound as a beige colored solid. Mp: 123.0-125.0 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.68 (m, 2), 1.78 (m, 4), 2.30 (s, 3), 3.42 (br s, 4), 3.66 (s, 3), 7.44-7.54 (m, 5), 8.61 (s, 1). MS m/z: 307 (M+1).

25

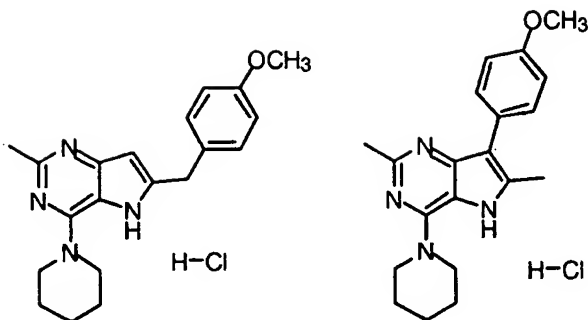
Example 156**4-Chloro-1-(((2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)methyl)sulfonyl)benzene Hydrochloride Hydrate.**

30

Using the method described in Example 30 by employing 1-[(2-pyrrolidinylprop-1-enyl)sulfonyl]-4-

chlorobenzene (freshly prepared before use from 4-chlorophenylsulfonylacetone (Lancaster Chemical Company), pyrrolidine and TiCl_4 (2.03 g, 7.10 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.47 g, 7.10 mmol), *N,N*-diisopropylethylamine (1.3 mL, 7.10 mmol), piperidine (1.1 mL, 11.4 mmol), NEt_3 (1.6 mL) and SnCl_2 (21 mL of a 2 M soln in DMF). In this example the mixture of enamine, 2-methyl-4,6-dichloro-5-nitropyrimidine and *N,N*-diisopropylethylamine was stirred at 100 °C for 20 h prior to piperidine addition. The SnCl_2 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 100% EtOAc as eluant to give 441 g (15%) of 4-chloro-1-[(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)methyl)sulfonyl]benzene as a brown colored solid. This compound (0.44 g, 1.08 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.10 mL, 1.10 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 296 mg (9%) of the title compound as a white colored solid. Mp: 199-201 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.57 (m, 4), 1.65 (m, 2), 2.47 (s, 3), 3.85 (br s, 4), 5.02 (s, 2), 6.23 (s, 1), 7.65 (AB q, 4, $J = 6.2, 6.2$), 12.20 (s, 1), 14.18 (s, 1). MS m/z : 405 ($M+1$ for free base). Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{ClN}_4\text{O}_2\text{S}\cdot\text{HCl}\cdot 0.9\text{H}_2\text{O}$: C, 49.87; H, 5.24; N, 12.25; Cl, 15.49. Found: C, 49.85; H, 5.17; N, 12.15; Cl, 15.61.

257



Example 157

Example 158

Example 157 and Example 158

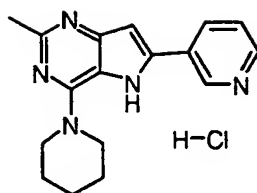
4-Methoxy-1-[(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)methyl]benzene Hydrochloride and 1-[2,6-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidin-7-yl]-4-methoxybenzene Hydrochloride Hydrate.

Using the method described in Example 30 by employing 1-[2-pyrrolidinylprop-1-enyl]-4-methoxy benzene (freshly prepared before use from 4-methoxy phenylacetone (Aldrich Chemical Company), pyrrolidine and TiCl_4 (3.06 g, 14.10 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.92 g, 14.10 mmol), *N,N*-diisopropylethylamine (2.5 mL, 14.10 mmol), piperidine (2.2 mL, 22.6 mmol), NEt_3 (3.1 mL) and SnCl_4 (42 mL of a 2 M soln in DMF). In this example the SnCl_4 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 578 g (12%) of 4-methoxy-1-[(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)methyl]benzene as a brown colored solid and 466 mg (10%) of 1-[2,6-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidin-7-yl]-4-methoxybenzene as a beige colored solid.

Example 157: 4-Methoxy-1-[(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)methyl]benzene (574 mg, 1.71 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to boiling. To the hot solution was added 1 M
5 ethereal HCl (1.70 mL, 1.70 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 488 mg (9%) of Example 157 as
10 tan colored crystals. Mp: 263-267 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.73 (br s, 6), 3.75 (s, 3), 4.01 (br s, 4), 4.15 (s, 2), 6.19 (s, 1), 6.94 (d, 2, J = 8.7), 7.27 (d, 2, J = 8.6), 12.02 (s, 1), 13.93 (s, 1). MS m/z: 337 (M+1 for free base). Anal. Calcd for
15 C₂₀H₂₄N₄O•HCl: C, 64.42; H, 6.76; N, 15.03; Cl, 9.51. Found: C, 64.41; H, 6.66; N, 15.00; Cl, 9.63.

Example 158: 1-[2,6-Dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidin-7-yl]-4-methoxybenzene (466 mg, 1.39 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and
20 heated to boiling. To the hot solution was added 1 M ethereal HCl (1.40 mL, 1.40 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under
25 vacuum at 60 °C to give 375 mg (7%) of Example 158 as a beige colored powder. Mp: 170 °C (dec). ¹H NMR (DMSO-d₆; 400 MHz): δ 1.62 (br s, 6), 2.36 (s, 3), 2.46 (s, 3), 3.76 (s, 3), 3.95 (br s, 4), 7.03 (d, 2, J = 8.7), 7.28 (d, 2, J = 8.6), 12.11 (s, 1), 13.27 (s, 1). MS
30 m/z: 337 (M+1 for free base). Anal. Calcd for C₂₀H₂₄N₄O•1.2HCl•0.9H₂O: C, 60.60; H, 6.87; N, 14.14; Cl, 10.73. Found: C, 60.74; H, 6.62; N, 14.01; Cl, 10.62.

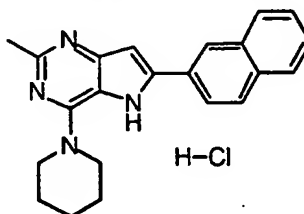
259

**Example 159****2-Methyl-4-piperidyl-6-(3-pyridyl)pyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

5 Using the method described in Example 30 by
employing 3-(1-pyrrolidinylvinyl)pyridine (freshly
prepared before use from 3-acetylpyridine (Aldrich
Chemical Company), pyrrolidine and TiCl_4 (1.95 g, 11.2
mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example
10 76(b)) (2.32 g, 11.2 mmol), *N,N*-diisopropylethylamine
(2.0 mL, 11.2 mmol), piperidine (1.8 mL, 17.9 mmol),
 NEt_3 (2.5 mL) and SnCl_2 (34 mL of a 2 M soln in DMF).
In this example the SnCl_2 solution was added to the
reaction mixture at 140 °C. The mixture was stirred at
15 140 °C for an additional 0.5 h then the heating was
discontinued and the mixture was allowed to cool to
room temperature. The mixture was stirred at room
temperature an additional 4 d. The residue was
purified by flash chromatography on silica gel with
20 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 0.90 mg (3%) of 2-
methyl-4-piperidyl-6-(3-pyridyl)pyrrolo[3,2-d]
pyrimidine as a beige colored solid. This compound (89
mg, 0.30 mmol) was dissolved in 10:1 EtOAc/MeOH (10 mL)
and heated to boiling. To the hot solution was added 1
25 M ethereal HCl (0.30 mL, 0.30 mmol). The solution was
allowed to cool to room temperature. The resulting
crystals were collected by filtration, washed with
 EtOAc (2 x 5 mL), Et_2O (3 x 5 mL) and dried under
vacuum at 60 °C to give 54 mg (2%) of the title
30 compound as a brown colored solid. Mp: >280 °C. ^1H NMR
($\text{DMSO}-d_6$; 500 MHz): δ 1.65 (br s, 6), 2.51 (s, 3),

260

- 4.02 (t, 4, $J = 5.4$), 6.96 (s, 1), 7.52 (dd, 1, $J = 7.9, 7.9$), 8.32 (d, 1, $J = 8.0$), 8.61 (d, 1, $J = 4.8$), 9.11 (d, 1, $J = 2.1$), 12.08 (s, 1), 14.29 (s, 1). MS m/z : 294 ($M+1$ for free base). Anal. Calcd for $C_{17}H_{19}N_5 \cdot 1.05HCl \cdot 1.5H_2O$: C, 56.90; H, 6.48; N, 19.52; Cl, 10.37. Found: C, 57.20; H, 6.23; N, 19.50; Cl, 10.39.

Example 160

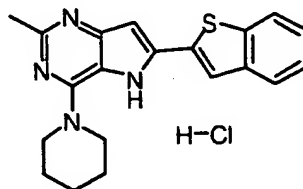
10 2-Methyl-6-(2-naphthyl)-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

- Using the method described in Example 30 by employing [1-(2-naphthyl)vinyl]pyrrolidine (freshly prepared before use from 2'-acetylnaphthone (Aldrich Chemical Company), pyrrolidine and $TiCl_4$ (1.91 g, 8.60 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.78 g, 8.60 mmol), *N,N*-diisopropylethylamine (1.5 mL, 8.6 mmol), piperidine (1.4 mL, 13.8 mmol), NEt_3 (1.9 mL) and $SnCl_4$ (23 mL of a 2 M soln in DMF).
- 20 In this example the $SnCl_4$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 2.5 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The mixture was stirred at room
- 25 temperature an additional 36 h. The residue was purified by flash chromatography on silica gel with 95:5 $CHCl_3/MeOH$ as eluant to give 1.25 g (55%) of 2-methyl-6-(2-naphthyl)-4-piperidylpyrrolo[3,2-d]pyrimidine as a beige colored solid. This compound
- 30 (1.25 g, 3.64 mmol) was dissolved in 5:1 EtOAc/MeOH (60 mL) and heated to boiling. To the hot solution was

261

added 1 M ethereal HCl (3.60 mL, 3.60 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 1.02 g (40%) of the title compound as a yellow colored powder. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.67 (br s, 6), 2.52 (s, 3), 4.04 (t, 4, J = 4.9), 6.98 (s, 1), 7.55 (m, 2), 7.94 (t, 1, J = 4.0), 8.00 (d, 1, J = 5.4), 8.02 (br s, 2), 8.50 (s, 1), 12.09 (s, 1), 14.27 (s, 1). MS m/z: 343 (M+1 for free base). Anal. Calcd for C₂₂H₂₂N₄•HCl•1.5H₂O: C, 65.09; H, 6.46; N, 13.81; Cl, 8.73. Found: C, 65.00; H, 6.45; N, 13.80; Cl, 8.76.

15

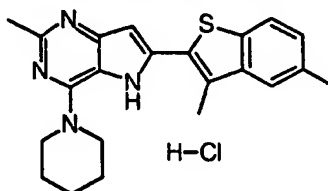
Example 161**2-[2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzo[b]thiophene Hydrochloride Hydrate.**

Using the method described in Example 30 by employing 2-(1-pyrrolidinylvinyl)benzo[b]thiophene (freshly prepared before use from 2-acetylbenzo[b]thiophene (Avocado Chemical Company), pyrrolidine and TiCl₄ (1.71 g, 7.45 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.54 g, 7.45 mmol), N,N-diisopropylethylamine (1.3 mL, 7.45 mmol), piperidine (1.2 mL, 11.9 mmol), NEt₃ (1.7 mL) and SnCl₂ (22 mL of a 2 M soln in DMF). In this example the SnCl₂ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue

262

was purified by flash chromatography on silica gel with 95:5 CHCl₃/MeOH as eluant to give 1.04 g (40%) of 2-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzo[b]thiophene as a yellow colored powder. This compound
5 (1.04 g, 2.98 mmol) was dissolved in 5:1 EtOAc/MeOH (50 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (3.00 mL, 3.00 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed
10 with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 0.88 g (31%) of the title compound as a yellow colored powder. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.66 (br s, 6), 2.51 (s, 3), 4.00 (br s, 4), 6.74 (s, 1), 7.39 (m, 2), 7.91 (t, 1, J = 6.9), 8.00 (t, 1, J = 4.0), 8.16 (s, 1), 12.22 (s, 1), 14.21 (s, 1). MS m/z: 349 (M+1 for free base).
15 Anal. Calcd for C₂₀H₂₀N₄S•HCl•0.70H₂O: C, 60.42; H, 5.68; N, 14.10; Cl, 8.92. Found: C, 60.38; H, 5.56; N, 13.93; Cl, 9.03.

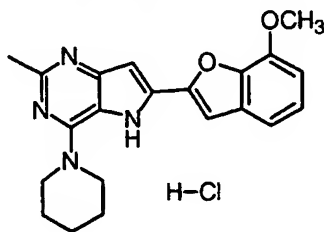
20

Example 162**3,5-Dimethyl-2-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzo[b]thiophene Hydrochloride****25 Monohydrate.**

Using the method described in Example 30 by employing 3,5-dimethyl-2-(1-pyrrolidinylvinyl)benzo[b]thiophene (freshly prepared before use from 2-acetyl-3,5-dimethyl[b]thiophene (Avocado Chemical Company),
30 pyrrolidine and TiCl₄ (1.81 g, 7.04 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.46 g,

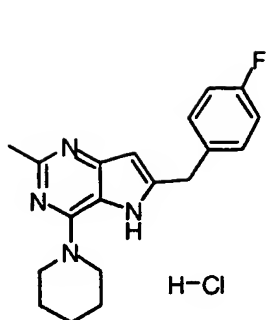
263

7.04 mmol), *N,N*-diisopropylethylamine (1.2 mL, 7.04 mmol), piperidine (1.1 mL, 11.3 mmol), NEt_3 (1.5 mL) and SnCl_2 (21 mL of a 2 M soln in DMF). In this example the SnCl_2 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 0.53 g (20%) of 3,5-dimethyl-2-[2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl]benzo[*b*]thiophene as a cream colored solid. This compound (530 mg, 1.41 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (1.50 mL, 1.50 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 493 mg (17%) of the title compound as a yellow colored solid. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.64 (br s, 6), 2.43 (s, 3), 2.44 (s, 3), 2.51 (s, 3), 3.98 (br s, 4), 6.65 (s, 1), 7.27 (d, 1, $J = 8.2$), 7.66 (s, 1), 7.87 (d, 1, $J = 8.3$), 12.31 (s, 1), 14.13 (s, 1). MS m/z : 377 ($M+1$ for free base). Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_4\text{S}\cdot\text{HCl}\cdot\text{H}_2\text{O}$: C, 61.31; H, 6.31; N, 13.00; Cl, 8.23. Found: C, 61.26; H, 5.92; N, 12.91; Cl, 8.32.

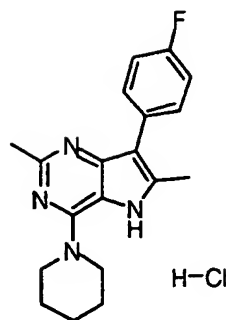
Example 163

7-Methoxy-2-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzo[b]furan Hydrochloride Hydrate.

Using the method described in Example 30 by employing 7-methoxy-2-(1-pyrrolidinylvinyl)benzo[b]furan (freshly prepared before use from 2-acetyl-7-methoxybenzo[b]furan (Avocado Chemical Company), pyrrolidine and TiCl_4 (1.89 g, 7.77 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (1.61 g, 7.77 mmol), *N,N*-diisopropylethylamine (1.4 mL, 7.77 mmol), piperidine (1.2 mL, 12.4 mmol), NEt_3 (1.7 mL) and SnCl_4 (23 mL of a 2 M soln in DMF). In this example the SnCl_4 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as eluant to give 0.27 g (10%) of 7-methoxy-2-[2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]benzo[b]furan as a brown colored powder. This compound (0.26 g, 0.72 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.80 mL, 0.80 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under vacuum at 60 °C to give 195 mg (7%) of the title compound as a yellow colored powder. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.66 (br s, 6), 2.51 (s, 3), 3.92 (s, 3), 4.01 (br s, 4), 6.88 (s, 1), 6.98 (d, 1, $J = 9.6$), 7.20 (t, 1, $J = 7.8$), 7.28 (d, 1, $J = 7.7$), 7.72 (s, 1), 12.31 (s, 1), 14.09 (s, 1). MS m/z : 363 ($M+1$ for free base). Anal. Calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_2 \cdot \text{HCl} \cdot 0.3\text{H}_2\text{O}$: C, 62.38; H, 5.88; N, 13.86; Cl, 8.77. Found: C, 62.31; H, 5.81; N, 13.60; Cl, 8.82.



Example 164



Example 165

Example 164 and Example 165

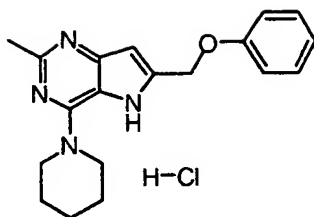
6-[(4-Fluorophenyl)methyl]-2-methyl-4-piperidylpyrrolo
 5 [3,2-d]pyrimidine Hydrochloride and 7-(4-Fluorophenyl)-
 2,6-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine
 Hydrochloride.

Using the method described in Example 30 by
 employing [2-(4-fluorophenyl)-1-methylvinyl]pyrrolidine
 10 (freshly prepared before use from (4-fluorophenyl)
 acetone (Aldrich Chemical Company), pyrrolidine and
 TiCl_4 (1.64 g, 8.00 mmol), 2-methyl-4,6-dichloro-5-
 nitropyrimidine (Example 76(b)) (1.66 g, 8.00 mmol),
 N,N -diisopropylethylamine (1.4 mL, 8.00 mmol),
 15 piperidine (1.3 mL, 12.8 mmol), NEt_3 (1.8 mL) and SnCl_4 ,
 (24 mL of a 2 M soln in DMF). In this example the
 SnCl_4 solution was added to the reaction mixture at 140
 $^\circ\text{C}$. The mixture was stirred at 140 $^\circ\text{C}$ for an additional
 16 h then the heating was discontinued and the mixture
 20 was allowed to cool to room temperature. The residue
 was purified by flash chromatography on silica gel with
 50:50 EtOAc/hexanes as eluant to give 108 g (4%) of 6-
 [(4-fluorophenyl)methyl]-2-methyl-4-piperidylpyrrolo
 [3,2-d]pyrimidine as a white colored solid and 172 mg
 25 (7%) of 7-(4-fluorophenyl)-2,6-dimethyl-4-piperidyl
 pyrrolo[3,2-d]pyrimidine as a white colored solid.

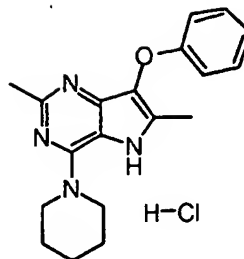
Example 164: 6-[(4-Fluorophenyl)methyl]-2-methyl-
 4-piperidylpyrrolo[3,2-d]pyrimidine (108 mg, 0.33 mmol)

was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.40 mL, 0.40 mmol). The solution was allowed to cool to room temperature. The resulting solid was
5 collected by filtration, washed with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 97 mg (3%) of Example 164 as a white colored solid.
Mp: 254-255 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.70 (br s, 6), 2.51 (s, 3), 3.98 (br s, 4), 6.21 (s, 1), 7.17
10 (t, 2, J = 8.9), 7.35 (dd, 2, J = 8.6, 8.5), 12.04 (s, 1), 13.90 (s, 1). MS m/z: 325 (M+1 for free base).
Anal. Calcd for C₁₉H₂₁FN₄•HCl: C, 63.24; H, 6.15; N, 15.42; Cl, 9.93. Found: C, 63.26; H, 6.15; N, 15.42; Cl, 9.93.

15 **Example 165:** 7-(4-Fluorophenyl)-2,6-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine (162 mg, 0.50 mmol) was dissolved in 5:1 EtOAc/MeOH (15 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.50 mL, 0.50 mmol). The solution was allowed to
20 cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 122 mg (5%) of Example 165 as a beige colored solid.
Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.63 (br s,
25 6), 2.37 (s, 3), 2.46 (s, 3), 3.95 (br s, 4), 7.30 (t, 2, J = 8.8), 7.40 (dd, 2, J = 8.5, 8.5), 12.10 (s, 1), 13.31 (s, 1). MS m/z: 325 (M+1 for free base). Anal. Calcd for C₁₉H₂₁FN₄•HCl: C, 63.24; H, 6.15; N, 15.53; Cl, 9.82. Found: C, 63.40; H, 6.22; N, 15.31; Cl, 9.94.



Example 166



Example 167

Example 166 and Example 167

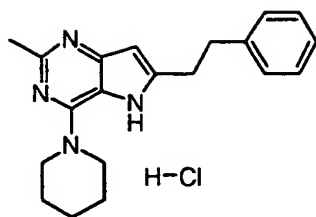
[(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)methoxy]benzene hydrochloride and 2,6-Dimethyl-7-phenoxy-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

Using the method described in Example 30 by employing [2-pyrrolidinylprop-2-enyloxy]benzene and [2-pyrrolidinylprop-1-enyloxy]benzene (freshly prepared before use from phenoxy-2-propanone (Aldrich Chemical Company), pyrrolidine and TiCl_4 (2.03 g, 13.50 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.79 g, 13.50 mmol), *N,N*-diisopropylethylamine (2.4 mL, 13.5 mmol), piperidine (2.2 mL, 21.6 mmol), NEt_3 (3.0 mL) and SnCl_4 (40 mL of a 2 M soln in DMF). In this example the SnCl_4 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 110 mg (3%) of [(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)methoxy]benzene as a brown colored gummy solid and 60 mg (1%) of 2,6-dimethyl-7-phenoxy-4-piperidylpyrrolo[3,2-d]pyrimidine as a yellow colored solid.

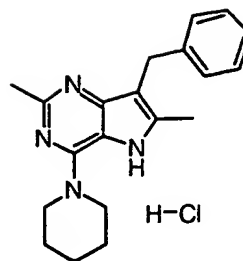
Example 166: [(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)methoxy]benzene (107 mg, 0.33 mmol) was dissolved in 5:1 EtOAc/MeOH (20 mL) and heated to

boiling. To the hot solution was added 1 M ethereal HCl (0.40 mL, 0.40 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 66 mg (2%) of Example 166 as a white colored solid. Mp: 238-239 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.64 (br s, 6), 2.48 (s, 3), 3.94 (br s, 4), 5.22 (s, 2), 6.66 (s, 1), 6.92 (t, 1, J = 7.3), 7.01 (d, 2, J = 7.9), 7.26 (dt, 2, J = 1.1, 7.4), 12.64 (s, 1), 14.18 (s, 1). MS m/z: 323 (M+1 for free base). Anal. Calcd for C₁₉H₂₂N₄O•HCl: C, 63.59; H, 6.46; N, 15.61; Cl, 9.88. Found: C, 63.48; H, 6.48; N, 15.51; Cl, 10.02.

Example 167: 2,6-Dimethyl-7-phenoxy-4-piperidyl pyrrolo[3,2-d]pyrimidine (57 mg, 0.18 mmol) was dissolved in 5:1 EtOAc/MeOH (6 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.20 mL, 0.20 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 45 mg (1%) of Example 167 as a beige colored powder. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.64 (br s, 6), 2.20 (s, 3), 2.43 (s, 3), 3.94 (br s, 4), 6.88 (d, 2, J = 8.3), 7.01 (t, 1, J = 7.0), 7.28 (t, 2, J = 7.4), 12.01 (s, 1), 13.84 (s, 1). MS m/z: 323 (M+1 for free base). Anal. Calcd for C₁₉H₂₂N₄O•HCl•0.75H₂O: C, 61.28; H, 6.63; N, 15.05; Cl, 9.52. Found: C, 61.25; H, 6.31; N, 14.73; Cl, 9.44.



Example 168



Example 169

Example 168 and Example 169

2-Methyl-6-(2-phenylethyl)-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate and 2,6-Dimethyl-7-benzyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

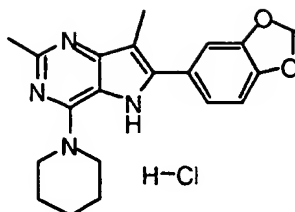
Using the method described in Example 30 by employing [1-(2-phenylethyl)vinyl]pyrrolidine and [1-(3-phenylprop-1-enyl)pyrrolidine (freshly prepared before use from benzylacetone (Aldrich Chemical Company), pyrrolidine and TiCl_4 (2.23 g, 11.3 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.34 g, 11.3 mmol), *N,N*-diisopropylethylamine (2.0 mL, 11.3 mmol), piperidine (1.8 mL, 18.1 mmol), NEt_3 (2.5 mL) and SnCl_2 (34 mL of a 2 M soln in DMF). In this example the SnCl_2 solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc/hexanes as eluant to give 500 mg (14%) of 2-methyl-6-(2-phenylethyl)-4-piperidylpyrrolo[3,2-d]pyrimidine as a brown colored solid and 181 mg (5%) of 2,6-dimethyl-7-benzyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a beige colored solid.

Example 168: 2-Methyl-6-(2-phenylethyl)-4-piperidylpyrrolo[3,2-d]pyrimidine (481 mg, 1.50 mmol) was dissolved in 5:1 EtOAc/MeOH (40 mL) and heated to

boiling. To the hot solution was added 1 M ethereal HCl (1.50 mL, 1.50 mmol). The solution was allowed to cool to room temperature. The resulting solid was collected by filtration, washed with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 271 mg (7%) of Example 168 as a beige colored powder. Mp: 236-238 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.60 (br s, 6), 2.45 (s, 3), 2.95 (t, 2, J = 8.4), 3.09 (t, 2, J = 8.4), 3.92 (br s, 4), 6.24 (s, 1), 7.11-7.14 (m, 1), 7.16-7.25 (m, 4), 11.88 (s, 1), 14.06 (s, 1). MS m/z: 321 (M+1 for free base). Anal. Calcd for C₂₀H₂₄N₄•HCl•0.25H₂O: C, 66.46; H, 7.11; N, 15.51; Cl, 9.81. Found: C, 66.40; H, 7.12; N, 15.37; Cl, 9.91.

Example 169: 2,6-Dimethyl-7-benzyl-4-piperidyl pyrrolo[3,2-d]pyrimidine (175 mg, 0.55 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to boiling. To the hot solution was added 1 M ethereal HCl (0.60 mL, 0.60 mmol). The solution was allowed to cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 60 °C to give 71 mg (2%) of Example 169 as a beige colored powder. Mp: >240 °C (dec). ¹H NMR (DMSO-d₆; 400 MHz): δ 1.61 (br s, 6), 2.28 (s, 3), 2.52 (s, 3), 3.91 (br s, 4), 4.07 (s, 2), 7.08-7.13 (m, 3), 7.20 (t, 2, J = 7.6), 11.99 (s, 1), 14.21 (s, 1). MS m/z: 321 (M+1 for free base). Anal. Calcd for C₂₀H₂₄N₄•HCl•0.4H₂O: C, 65.97; H, 7.14; N, 15.39; Cl, 9.74. Found: C, 66.04; H, 6.98; N, 15.37; Cl, 9.79.

271

**Example 170****5-[2,7-Dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-2H-benzo[d]1,3-dioxolane Hydrochloride Hydrate.**

5 Using the method described in Example 30 by
employing 5-(1-pyrrolidinyprop-1-enyl)-2H-benzo[d]1,3-
dioxolene (freshly prepared before use from 3,4-
methylenedioxypropiphenone (Lancaster Chemical
Company), pyrrolidine and TiCl_4 (2.03 g, 8.78 mmol), 2-
10 methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b))
(1.82 g, 8.78 mmol), *N,N*-diisopropylethylamine (1.5 mL,
8.78 mmol), piperidine (1.4 mL, 14.1 mmol), NEt_3 (2.0
mL) and SnCl_2 (26 mL of a 2 M soln in DMF). In this
example the SnCl_2 solution was added to the reaction
15 mixture at 140 °C. The mixture was stirred at 140 °C
for an additional 16 h then the heating was
discontinued and the mixture was allowed to cool to
room temperature. The residue was purified by flash
chromatography on silica gel with 95:5 $\text{CHCl}_3/\text{MeOH}$ as
20 eluant to give 247 mg (8%) of 5-[2,7-dimethyl-4-
piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-2H-benzo[d]1,3-
dioxolane as a beige colored solid. This compound (241
mg, 0.69 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL)
and heated to boiling. To the hot solution was added 1
25 M ethereal HCl (0.70 mL, 0.70 mmol). The solution was
allowed to cool to room temperature. The resulting
crystals were collected by filtration, washed with
EtOAc (2 x 10 mL), Et_2O (3 x 15 mL) and dried under
vacuum at 60 °C to give 165 mg (5%) of the title
30 compound as a beige colored powder. Mp: 268-269 °C. ^1H
NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.63 (br s, 6), 2.24 (s, 3),

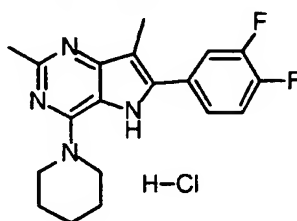
2.54 (s, 3), 3.96 (br s, 4), 6.07 (s, 2), 7.05-7.11 (m, 2), 7.05 (d, 1, $J = 1.3$), 11.76 (s, 1), 13.89 (s, 1).

MS m/z : 351 ($M+1$ for free base). Anal. Calcd for

$C_{20}H_{22}N_4O_2 \cdot HCl \cdot 0.4H_2O$: C, 60.95; H, 6.09; N, 14.22; Cl,

5 9.00. Found: C, 60.99; H, 5.88; N, 14.19; Cl, 9.09.

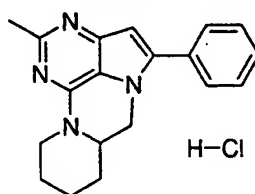
Example 171



6-(3,4-Difluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.

10 Using the method described in Example 30 by employing [1-(3,4-difluorophenyl)prop-1-enyl] pyrrolidine (freshly prepared before use from 3,4-difluoropropiophenone (Lancaster Chemical Company),
15 pyrrolidine and $TiCl_4$ (2.27 g, 10.2 mmol), 2-methyl-4,6-dichloro-5-nitropyrimidine (Example 76(b)) (2.11 g, 10.2 mmol), N,N -diisopropylethylamine (1.8 mL, 10.2 mmol), piperidine (1.6 mL, 16.3 mmol), NEt_3 (2.3 mL) and $SnCl_2$ (31 mL of a 2 M soln in DMF). In this
20 example the $SnCl_2$ solution was added to the reaction mixture at 140 °C. The mixture was stirred at 140 °C for an additional 16 h then the heating was discontinued and the mixture was allowed to cool to room temperature. The residue was purified by flash
25 chromatography on silica gel with 95:5 $CHCl_3/MeOH$ as eluant to give 305 mg (9%) of 6-(3,4-difluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine as a brown colored oil. This compound (304 mg, 0.89 mmol) was dissolved in 5:1 EtOAc/MeOH (30 mL) and heated to
30 boiling. To the hot solution was added 1 M ethereal HCl (0.90 mL, 0.90 mmol). The solution was allowed to

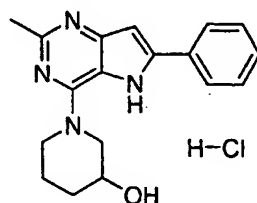
cool to room temperature. The resulting crystals were collected by filtration, washed with EtOAc (2 x 10 mL), Et₂O (3 x 15 mL) and dried under vacuum at 60 °C to give 201 mg (5%) of the title compound as a beige colored powder. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.63 (br s, 6), 2.27 (s, 3), 2.56 (s, 3), 3.98 (br s, 4), 7.47-7.49 (m, 1), 7.61 (q, 1, J = 8.6), 7.78 (dt, 1, J = 1.4, 7.8), 11.96 (s, 1), 14.08 (s, 1). MS m/z: 343 (M+1 for free base). Anal. Calcd for C₁₉H₂₀F₂N₄•1.1HCl: C, 59.64; H, 5.56; N, 14.65; Cl, 10.22. Found: C, 59.59; H, 5.56; N, 14.67; Cl, 10.02.

Example 172

2-Methyl-5-phenyl-7,7a,8,9,10,11-hexahydro-1,3,11a-triaza-pyrrolo[3,2,1-de]phenanthridine Hydrochloride monohydrate.

A solution of 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-d]pyrimidine (1.0 g, 4.1 mmol, Example 1e) and 2-hydroxymethyl piperidine (Aldrich Chemical Company) (0.49 g, 4.2 mmol) in N-methyl morpholine (10 mL) was heated at 110 °C for 12 h. The solvent was concentrated *in vacuo* and the residue was mixed with POCl₃ (5 mL, 54 mmol) and toluene (20 mL). The mixture was heated at reflux for 6.5 h before it was concentrated *in vacuo*. The residue was taken up in CH₂Cl₂ (50 mL)-H₂O (50 mL) and the pH of the aqueous phase was adjusted to pH ~8 with NaOH solution (2 N). The organic phase was separated and the aqueous phase was extracted with CH₂Cl₂ (3 x). The combined organic phase was dried over Na₂SO₄, concentrated *in vacuo*, and

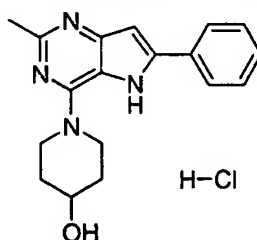
the resulting residue was purified by flash chromatography on silica gel (MeOH in CH₂Cl₂, 1-15%). The free base was treated with ethereal HCl to give the title compound as the HCl salt (0.18 g, 14%). Mp: >280 °C. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.58-1.66 (m, 3), 1.85-1.91 (m, 2), 2.05 (d, 1, *J* = 10), 2.55 (s, 3), 3.43 (t, 1, *J* = 10), 4.22-4.25 (m, 2), 4.77 (t, 1, *J* = 14), 4.86 (d, 1, *J* = 13), 7.10 (s, 1), 7.49-7.57 (m, 3), 8.02 (d, 2, *J* = 8). MS *m/z*: 305 (M+1). Anal. Calcd for C₁₉H₂₀N₄•2HCl•H₂O: C, 57.72; H, 6.12; N, 14.18; Cl, 17.95. Found: C, 57.69; H, 6.24; N, 14.02; Cl, 17.79.

Example 173**15 1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidine-4-yl)piperidin-3-ol Hydrochloride Hydrate.**

A solution of 2-methyl-4-chloro-6-phenyl pyrrolo [3,2-d]pyrimidine (0.6 g, 2.5 mmol, Example 1e), 3-hydroxy piperidine hydrogen chloride (Aldrich Chemical Company) (0.34 g, 2.5 mmol), and iso-Pr₂NEt (1.0 mL) in toluene was heated at reflux for 24 h. The mixture was allowed to cool to room temperature and was treated with aqueous NaOH (0.5 N, 10 mL). The slurry was filtered, and the solid was washed with CH₂Cl₂ (3 x 5 mL). The solid was dissolved in a mixture of CH₂Cl₂ (5 mL) plus a minimum amount of MeOH and the solution was treated with HCl (2 mL, 1 N in ether). The resulting mixture was filtered and the solid was triturated with hot EtOAc to afford the title compound as a white solid (0.54 g, 71%). ¹H NMR (DMSO-d₆; 400 MHz): δ 1.44-1.66 (m, 2), 1.74-1.80 (m, 2), 2.58 (s, 3), 3.76 (br s, 2),

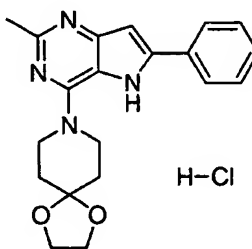
275

3.99 (br s, 1), 4.30 (d, br d, $J = 12$), 5.15 (br s, 0.5), 6.89 (s, 1), 7.44–7.57 (m, 3), 7.98 (d, 2, $J = 7.2$), 11.90–11.98 (br s, 1). MS m/z : 308 (M+1). Anal. Calcd for $C_{18}H_{20}N_4O \cdot 1.19HCl \cdot 0.34H_2O$: C, 60.38; H, 6.16; N, 15.65; Cl, 11.80. Found: C, 60.38; H, 5.91; N, 15.61; Cl, 11.83.

Example 174

10 **1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidine-4-yl)**
piperidin-4-ol Hydrochloride Hydrate.

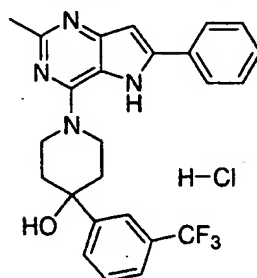
The title compound was prepared according to the procedure described in Example 173, using 4-hydroxy piperidine (Aldrich Chemical Company) (0.26 g, 2.57 mmol) and 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-d]pyrimidine (Example 1e) (0.49 g, 2.0 mmol), as a white solid (0.30 g, 48%). 1H NMR (DMSO- d_6 ; 400 MHz): d 1.51–1.59 (m, 2), 2.58 (s, 3), 3.78–3.90 (m, 3), 4.34–4.37 (m, 2), 6.89 (s, 1), 7.49–7.57 (m, 3), 7.96 (d, 2, $J = 7.2$), 11.8 (br s, 1). MS m/z : 308 (M+1). Anal. Calcd for $C_{18}H_{20}N_4O \cdot HCl \cdot 0.33H_2O$: C, 61.62; H, 5.94; N, 15.97; Cl, 10.10. Found: C, 61.62; H, 5.91; N, 15.81; Cl, 10.28.



25

Example 175**8-Aza-8-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidine-4-yl)-1,4-dioxaspiro[4,5]decane Hydrochloride Hydrate.**

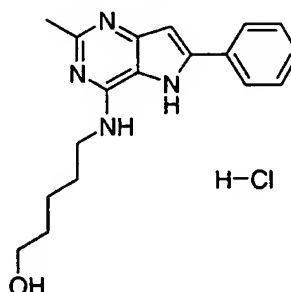
The title compound was prepared according to the procedure described in Example 173, using 1,4-dioxaspiro[4,5]decane (Aldrich Chemical Company) (0.35 g, 2.50 mmol) and 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-d]pyrimidine (Example 1e) (0.60 g, 2.47 mmol), as a white solid (0.46 g, 53%). ¹H NMR (DMSO-d₆; 400 MHz): d 1.83 (br t, 4), 2.58 (s, 3), 3.97 (s, 4), 4.12 (br t, 4), 6.93 (s, 1), 7.50-7.6 (m, 3), 7.96 (d, 2, J = 6.8), 12.0 (br s, 1). MS m/z: 350 (M+1). Anal. Calcd for C₂₀H₂₂N₄O₂•1.01HCl•0.3H₂O: C, 61.18; H, 6.06; N, 14.27; Cl, 9.13. Found: C, 61.18; H, 5.76; N, 14.35; Cl, 9.36.

Example 176**1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidine-4-yl)-4-[3-(trifluoromethyl)phenyl]piperidin-4-ol Hydrochloride Hydrate.**

The title compound was prepared according to the procedure described in Example 173, using 4-[3-(trifluoromethyl)phenyl]-4-piperidinol hydrochloride (Acros Organics) (0.6 g, 2.1 mmol) and 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-d]pyrimidine (Example 1e) (0.42 g, 1.73 mmol), as a white solid (0.5 g, 59%). ¹H NMR (DMSO-d₆; 400 MHz): d 1.83 (d, 2, J = 13), 2.18 (t, 2, J = 11), 2.59 (s, 3), 3.73 (br s, 2), 4.81 (br s, 2), 5.70 (s, 1), 6.93 (s, 1), 7.49-7.62 (m, 5),

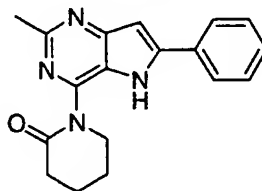
277

7.83 (d, 1, $J = 7.6$), 7.89 (s, 1), 7.97 (d, 2, $J = 7.6$). MS m/z : 453 (M+1). Anal. Calcd for $C_{25}H_{23}F_3N_4O \cdot 1.17HCl \cdot 0.17H_2O$: C, 60.25; H, 4.96; N, 11.25; Cl, 8.33. Found: C, 60.25; H, 5.16; N, 10.88; Cl, 8.18.

Example 177

5-[(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidine-4-yl)aminopentanol] Hydrochloride Hydrate.

The title compound was prepared according to the procedure described in Example 173, using 5-amino-1-pentanol (Fluka Chemika) (0.35 g, 3.4 mmol) and 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-d]pyrimidine (Example 1e) (0.42 g, 1.73 mmol), as a white solid (0.36 g, 61%). 1H NMR (DMSO- d_6 ; 400 MHz): δ 1.46 (br s, 4), 1.68 (bs, 2), 2.58 (s, 3), 3.62 (br s, 2), 4.40 (br s, 1), 6.93 (s, 1), 7.46-7.54 (m, 3), 8.05 (br, 2), 9.61 (s, 1), 13.47 (s, 1). MS m/z : 311 (M+1). Anal. Calcd for $C_{18}H_{22}N_4O \cdot HCl \cdot 0.28H_2O$: C, 61.42; H, 6.75; N, 15.92; Cl, 10.07. Found: C, 61.42; H, 6.67; N, 15.75; Cl, 10.17.

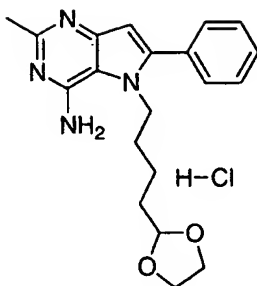
Example 178

25

**1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidine-4-yl)
piperidin-2-one.**

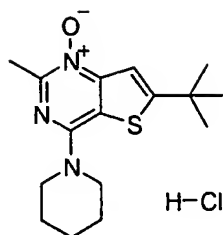
Phenyl-5-[(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidine-4-yl)amino]pentanoate. A mixture of 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-d]pyrimidine (Example 1e) (1.0 g, 4.11 mmol), 5-aminovaleric acid (Aldrich Chemical Company) (0.78 g, 0.66 mmol), and phenol (1.0 g, 10.6 mmol) was heated at 150 °C for 24 h. The mixture was let cool to room temperature and was treated with 5 mL each of EtOAc and ether. The mixture was filtered and the solid was washed with ether (3x) to give a light yellow solid (1.15 g). A solution of this intermediate (0.2 g), EDCI-HCl (Aldrich Chemical Company) (0.32 g, 1.7 mmol), and a catalytic amount of 4-dimethylaminopyridine in CH₂Cl₂/DMF/pyridine (5:2:2 mL) was stirred at room temperature overnight. EtOAc (50 mL) was added and the resulting mixture was washed with H₂O (3x). The combined aqueous phase was back extracted with ether (1x) and the combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel with 6% NH₃ (2N solution in MeOH) in CH₂Cl₂ to give the title compound as a white solid (0.018 g, 8%). ¹H NMR (CDCl₃; 400 MHz): δ 1.96-2.13 (m, 4), 2.66-2.89 (m, 5), 4.17 (t, 2, J = 5.6), 6.86 (d, 1, J = 2.0), 7.38-7.54 (m, 3), 7.74 (d, 2, J = 8.0), 9.68 (s, 1). MS m/z: 307 (M+1). HPLC (H₂O/CH₃CN, 50:50): R_f 1.444, >97% pure.

279

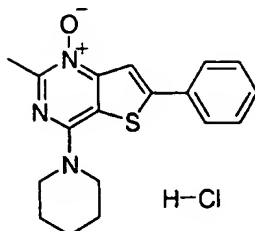
**Example 179****5-(4-(1,3-Dioxolan-2-yl)butyl)-2-methyl-6-phenyl
pyrrolo[3,2-d]pyrimidine-4-ylamine Hydrochloride.**

5 A solution of 2-methyl-4-amino-6-phenyl pyrrolo
[3,2-d]pyrimidine (Example 22) (0.079 g, 0.35 mmol), 2-
(1-chlorobutyl)-1,3-dioxolane (Fluka Chemika) (0.14 g,
0.85 mmol), and *iso*-Pr₃NEt (0.3 mL, 1.7 mmol) in
toluene/DMF (2.5:1.0 mL) was heated at reflux for 6
10 days. The mixture was allowed to cool to room
temperature and purified by flash chromatography on
silica gel with 5% NH₃ (2N in MeOH) 5% MeOH in CH₂Cl₂ to
afford the product. The product was dissolved in
CH₂Cl₂/EtOAc (1:1) and the solution was treated with a 2
15 M ethereal HCl (2 mL). The resulting slurry was
filtered, and the solid was washed with hot EtOAc (3x)
to give a yellow solid (29 mg, 23%). ¹H NMR (DMSO-*d*₆;
400 MHz): δ 1.53 (m, 2), 1.64 (m, 2), 1.84 (m, 2),
2.68 (s, 3), 3.86 (m, 2), 4.32 (br t, 2), 4.80 (t, 1),
20 7.34 (s, 1), 7.48-7.58 (m, 3), 8.11 (d, 2), 8.89 (s,
1), 9.17 (s, 1), 13.90 (s, 1). MS *m/z*: 353 (M+1).
Anal. Calcd for C₂₀H₂₄N₄O₂ • 2HCl: C, 56.47; H, 6.16; N,
13.18. Found: C, 56.36; H, 6.08; N, 13.21.

280

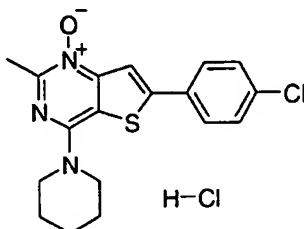
**Example 180****6-(*tert*-Butyl)-2-methyl-4-piperidylthiopheno[3,2-*d*]pyrimidin-1-ol Hydrochloride.**

- 5 A solution of 6-(*tert*-butyl)-2-methyl-4-piperidylthiopheno[3,2-*d*]pyrimidine (Example 34) (0.207 g, 0.716 mmol) in CH₂Cl₂ (5 mL) was treated with *meta*-chloro perbenzoic acid (Aldrich Chemical Company) (0.5 g, 2.9 mmol, 57-86% pure) and the reaction mixture was stirred
- 10 at room temperature for 3 days. The reaction mixture was treated with aqueous NaOH (0.5 N, 10 mL) and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3x) and the combined organic phase was dried over Na₂SO₄, and concentrated in *vacuo*.
- 15 The resulting residue was purified by flash chromatography on silica with MeOH in CH₂Cl₂ (0-10%) to give the product as a yellow solid (0.047 g, 21%). The product was dissolved in CH₂Cl₂ (1.0 mL) and the solution was treated with HCl (1 N in ether, 1.0 mL).
- 20 The resulting solution was left capped at room temperature for 3 days whereby large yellow crystals were formed. The solvent was decanted and the crystals were washed with 1:1 EtOAc-hexanes (3x) to give the title compound (~15 mg). Mp: 202-203 °C (dec). ¹H NMR
- 25 (CDCl₃; 400 MHz): δ 1.47 (s, 9), 1.80 (br s, 6), 2.85 (s, 3), 4.05 (br s, 4), 7.46 (s, 1), 13.89 (br s, 1). MS *m/z*: 306 (M+1). Anal. Calcd for C₁₆H₂₃N₃OS·HCl: C, 56.2; H, 7.08; N, 12.29; S, 9.38. Found: C, 55.96; H, 6.99; N, 12.15; Cl, 15.51. The structure was confirmed
- 30 by x-ray crystallography.

Example 181

5 **2-Methyl-6-phenyl-4-piperidylthiopheno[3,2-d]pyrimidin-1-ol Hydrochloride**

The oxidation was performed in a similar fashion as described in Example 180, using 240 mg (0.78 mmol) of 2-methyl-6-phenyl-4-piperidylthiopheno[3,2-d]pyrimidine (Example 32) and 240 mg (1.39 mmol, 57-86%)
10 of *meta*-chloroperbenzoic acid to afford the product (76 mg, 30%). The product was dissolved in 2.0 mL of CH₂Cl₂ and the solution was treated with 0.3 mL of HCl (2N in ether). The solid was collected and was washed with hot EtOAc (3x) to give the title compound as a yellow
15 solid (54 mg). ¹H NMR (DMSO-d₆; 400 MHz): δ 1.73 (s, 6), 2.69 (s, 3), 4.06 (br s, 4), 7.56 (br s, 3), 7.99 (br s, 2), 8.09 (s, 1). MS *m/z*: 326 (M+1).

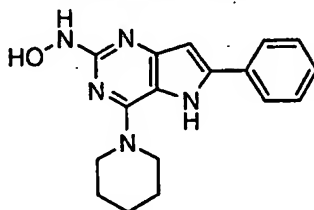
Example 182

20

6-(4-Chloro-phenyl)-2-methyl-4-piperidylthiopheno[3,2-d]pyrimidin-1-ol Hydrochloride Hydrate.

The oxidation was performed in a similar fashion as described in Example 180, using 246 mg (0.72 mmol)
25 of 6-(4-chloro-phenyl)-2-methyl-4-piperidylthiopheno[3,2-d]pyrimidine (Example 33) and 250 mg of *meta*-

chloroperbenzoic acid (1.45 mmol, 57-80%), to afford the product (156 mg, 60%). A total of 226 mg of the product were dissolved in 2.5 mL of CH_2Cl_2 and the solution was treated with 0.3 mL of HCl (2N in ether).
5 The solid was collected and washed with hot EtOAc (3x) to give the title compound as a yellow solid (87 mg).
 ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.73 (br s, 6), 2.69 (s, 3), 4.07 (br s, 4), 6.84 (s, 1), 7.63 (d, 2, $J = 8.4$), 8.01 (d, 2, $J = 8.4$), 8.15 (s, 1). MS m/z : 360, 362.
10 Anal. Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_3\text{ClOS} \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 53.33; H, 4.97; N, 10.37; S, 7.71; Cl, 17.49. Found: C, 53.00; H, 4.77; N, 10.21; S, 7.70; Cl, 15.51.

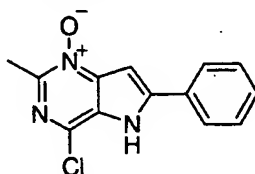
Example 183

15

6-Phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-yl hydroxylamine Hydrochloride.

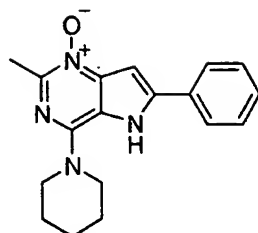
To a sealed 3-mL vial was 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 203(c)) (59
20 mg, 0.189 mmol), hydroxylamine hydrochloride (Aldrich Chemical Company) (52.5 mg, 0.754 mmol) and pyridine (1.0 mL). The solution was heated at 100 °C for 4 h. The reaction mixture was allowed to cool to room temperature and pyridine was removed in vacuo. The
25 resulting residue was washed with sat. NaHCO_3 , and extracted with CHCl_3 three times. The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The resulting crude oil was purified by flash chromatography on silica gel with
30 $\text{MeOH}/\text{CH}_2\text{Cl}_2/\text{NH}_4\text{OH}$ (4:95:1) as eluant to afford 35 mg (60 %) of a light-brown solid. The free base (35 mg, 0.113

mmol) was dissolved in hot MeOH (2 mL) and anhydrous ethereal HCl (0.113 mL of a 2 M soln, 0.226 mmol) was added dropwise. The precipitate was collected by filtration, washed with EtOAc/ether (1:1) (3 x 0.5 mL) and dried over vacuum to give 25 mg (58 %) of the title compound as a light brown solid. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.40-1.50 (m, 6), 3.70-3.80 (m, 4), 6.48 (s, 1), 7.30-7.80 (m, 5), 9.72 (s, 0.5), 10.50 (s, 0.5), 11.46 (s, 0.5), 12.44 (s, 0.5). MS *m/z* : 310 (M+1).
10 Anal. Calcd for C₁₇H₁₉N₅O•2HCl: C, 53.41; H, 5.54; N, 18.32. Found: C, 54.37; H, 6.16; N, 17.86.

Example 184**15 (a) 4-Chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidin-1-ol.**

To a solution of 2-methyl-4-chloro-6-phenyl pyrrolo[3,2-*d*]pyrimidine (Example 1e) (0.30 g, 1.23 mmol) in CH₂Cl₂ (5 mL) was added meta-chloroperbenzoic acid (Aldrich Chemical Company) (0.48 g, 2.79 mmol, 57-86%). The mixture was stirred at room temperature for 12 h whereby it was filtered. The solid was further washed with ether (3x) to afford the product as a yellow solid. ¹H NMR (MeOH-*d*₄; 400 MHz): δ 2.60 (s, 3), 7.30 (s, 1), 7.47-7.56 (m, 3), 8.12 (d, 2, *J* = 7.4), 12.4-13.1 (br s, 1). MS *m/z*: 259 (M+1).
25

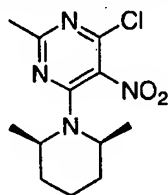
284



(b) 2-Methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidin-1-ol.

A solution of the chloride intermediate, prepared
 5 in Example 184(a), (0.178g, 0.69 mmol), and piperidine
 (0.50 mL, 5 mmol) in DMF (2.0 mL) was heated at 80 °C
 for 4 h. The solution was allowed to cool to room
 temperature and was diluted with EtOAc (~20 mL). The
 resulting mixture was washed with aqueous NaOH (0.5 M,
 10 mL), dried over Na₂SO₄, and concentrated in vacuo.
 Purification by flash chromatography on silica gel with
 NH₃ (2 N in MeOH)-MeOH in CH₂Cl₂ (0-5%), followed by
 preparative TLC with NH₃ (2 N in MeOH)-MeOH in CH₂Cl₂
 (2.5-5%), give the product (43 mg, 20%), which was
 15 crystallized from MeOH/EtOAc (1:4) as light yellow
 plates. Mp: 169-170 °C; ¹H NMR (MeOH-d₄; 400 MHz): δ
 1.78 (s, 6), 2.65 (s, 3), 4.06 (br s, 4), 6.93 (s, 1),
 7.32-7.54 (m, 3), 7.82 (d, 2, J = 10.8). MS m/z: 309
 (M+1). The structure was determined to be the
 20 monohydrate by x-ray crystallography.

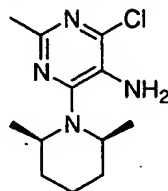
Example 185



(a) 4-((6S, 2R)-2,6-Dimethylpiperidyl)-6-chloro-2-methyl-5-nitropyrimidine.

25

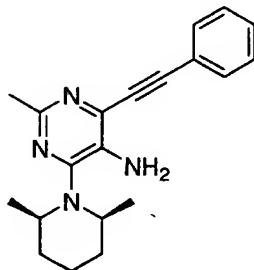
To a solution of 4,6-dichloro-2-methyl-5-nitro pyrimidine (Example 76 (b)) (2.44 g, 11.78 mmol, 1.0 eq) and triethylamine (Aldrich Chemical Company, 2.38 g, 23.56 mmol, 2.0 eq) in THF (12 mL) was added a solution of *cis*-2,6-dimethylpiperidine (Aldrich Chemical Company, 1.59 g, 11.78 mmol, 1.0 eq) in THF (12 mL) slowly. The final reaction mixture was stirred at room temperature for 3 days. After the removal of solvent *in vacuo*, the crude material was purified by flash chromatography on silica gel with 0-10% EtOAc/hexanes as eluant to afford the title compound (2.80 g, 84%) as a brown solid. ¹H NMR (CDCl₃, 500 MHz): d 1.29 (d, 6, *J* = 7.0), 1.56 (m, 1), 1.60-1.63 (m, 2), 1.73 (m, 2), 1.84-1.90 (m, 1), 2.50 (s, 3), 4.42 (m, 2). MS *m/z*: 285 (M+H)⁺; *m/z*: 283 (M-H)⁺.



(b) 4-((6*S*, 2*R*)-2,6-Dimethylpiperidyl)-6-chloro-2-methylpyrimidine-5-ylamine.

To a solution of 4-((6*S*, 2*R*)-2,6-dimethyl piperidyl)-6-chloro-2-methyl-5-nitropyrimidine (Example 185(a)) (2.26 g, 7.94 mmol, 1.0 eq) in anhydrous diethyl ether (15 mL) was added a freshly prepared solution of SnCl₄·H₂O (Aldrich Chemical Company, 32 mL, 2.0 M in concentrated aqueous HCl) slowly under N₂ at 0 °C. The reaction mixture was stirred at room temperature for 3 h, and then was poured onto a ice bath containing NaOH (12 g). The aqueous phase was extracted with EtOAc (100 mL x 4). The water phase was passed through a pad of Celite® and was extracted again with EtOAc (100 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude material was purified by flash

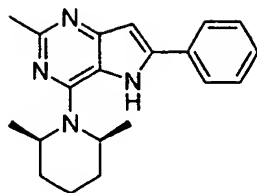
chromatography on silica gel with 0-50% EtOAc/hexanes as eluant to afford the title compound (795 mg, 40%) as a yellow oil. ¹H NMR (CDCl₃, 400 MHz): δ 0.75 (d, 6, *J* = 6.2), 1.31-1.34 (m, 2), 1.50-1.60 (m, 1), 1.72-1.76 (m, 3), 2.55 (s, 3), 3.03-3.07 (m, 2) 4.34 (br s, 2). MS *m/z*: 255 (M+H).



(c) 4-((6*S*, 2*R*)-2,6-Dimethylpiperidyl)-2-methyl-6-(2-phenylethynyl)pyrimidine-5-ylamine.

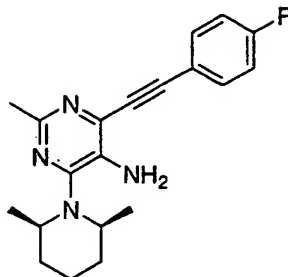
10 A mixture of 4-((6*S*, 2*R*)-2,6-dimethylpiperidyl)-6-chloro-2-methylpyrimidine-5-ylamine (Example 185(b)) (347 mg, 1.36 mmol, 1.0 eq), phenylacetylene (Aldrich Chemical Company, 279 mg, 2.73 mmol, 2.0 eq), Pd(PPh₃)₂Cl₂ (Aldrich Chemical Company, 48 mg, 0.068 mmol, 0.05 eq) and CuI (Aldrich Chemical Company, 13 mg, 0.068 mmol, 0.05 eq) in triethylamine (3 mL) was stirred under N₂ at 70 °C overnight. Upon cooling to room temperature, the reaction mixture was diluted with CHCl₃ (50 mL), passed through a pad of Celite® and
20 concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel with 0-8% EtOAc/hexanes as eluant to afford the title compound (412 mg, 95%) as a cherry colored semi-solid. ¹H NMR (CDCl₃, 400 MHz): δ 0.78 (d, 6, *J* = 6.2), 1.25-1.40 (m, 2), 1.50-1.60 (m, 1), 1.74-1.77 (m, 3), 2.59 (s, 3), 4.57 (br s, 2), 7.38 (m, 3), 7.60 (m, 2). MS *m/z*: 321 (M+H).

287



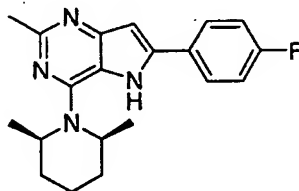
**(d) 4-((6*S*, 2*R*)-2,6-Dimethyl)-2-methyl-6-phenylpyrrolo
[3,2-*d*]pyrimidine Hydrochloride:**

A solution of 4-((6*S*,2*R*)-2,6-dimethylpiperidyl)-2-methyl-6-(2-phenylethynyl)pyrimidine-5-ylamine (Example 185(c)) (387 mg, 1.21 mmol) and CuI (Aldrich Chemical Company, 21 mg, 0.121 mmol, 0.1 eq) in anhydrous DMF (3 mL) was stirred under N₂ at 110 °C overnight. Upon cooling to the room temperature, the reaction mixture was diluted with CH₂Cl₂ (50 mL), passed through a pad of Celite® and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel with 0-80% EtOAc/hexanes as eluant to afford the free base of the product as a brown solid (200 mg, 50%). Mp: 223-225 °C. ¹H NMR (CDCl₃, 400 MHz): δ 1.28 (d, 6, *J* = 6.8), 1.61-1.70 (m, 3), 1.81-1.96 (m, 3), 2.61 (s, 3), 4.63 (br s, 2), 6.78 (s, 1), 7.39 (t, 1, *J* = 7.3), 7.48 (t, 2, *J* = 7.3), 7.66 (d, 2, *J* = 7.3), 8.39 (s, 1). MS *m/z*: 321 (M+H). The above material (195 mg, 0.61 mmol, 1.0 eq) was dissolved in diethyl ether (20 mL) and HCl (0.64 ml of a 1.0 M soln in ether, 0.64 mmol, 1.05 eq) was added dropwise. After stirring at room temperature for 10 min, the solution was concentrated in vacuo. Recrystallization from MeOH afforded the title compound (127 mg, 65%) as an off-white solid. Mp: >270 °C. ¹H NMR (DMSO-*d*₆, 400 MHz): δ 1.34 (d, 6, *J* = 6.7), 1.59 (m, 1), 1.78 (m, 4), 1.94 (m, 1), 2.61 (s, 3), 14 (br s, 2), 6.88 (s, 1), 7.51-7.59 (m, 3), 7.95 (d, 2, *J* = 6.8), 11.60 (s, 1), 14.28 (s, 1). MS *m/z*: 321 (M+H). Anal. Calcd for C₂₀H₂₄N₄·HCl: C, 67.31; H, 7.06; N, 15.70. Found: C, 67.04; H, 6.97; N, 15.60.

Example 186

5 **(a) 4-((6S, 2R)-2,6-Dimethylpiperidyl)-6-[2-(4-fluoro
phenyl)ethynyl]-2-methylpyrimidine-5-ylamine.**

This compound was synthesized by the method described in Example 185(c) from 4-((6S, 2R)-2,6-dimethylpiperidyl)-6-chloro-2-methylpyrimidine-5-ylamine (Example 185(b)) (449 mg, 1.76 mmol, 1.0 eq)
10 and 1-ethynyl-4-fluorobenzene (Aldrich Chemical Company, 500 mg, 4.16 mmol, 2.36 eq). The title compound was obtained as a brown solid (381 mg, 64%).
Mp: 134-136 °C. ¹H NMR (CDCl₃, 400 MHz): d 0.78 (d, 6, J = 6.2), 1.25-1.40 (m, 2), 1.50-1.60 (m, 1), 1.70-1.80
15 (m, 3), 2.59 (s, 3), 3.05-3.15 (m, 2), 4.55 (br s, 2), 7.05-7.09 (m, 2), 7.57-7.60 (m, 2). MS m/z: 339 (M+H).

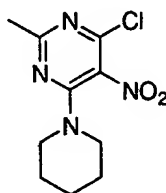


20 **(b) 4-((6S, 2R)-2,6-Dimethylpiperidyl)-6-(4-fluorophenyl)-2-methylpyrrolo[3,2-d]pyridine
Hydrochloride Monohydrate.**

This compound was synthesized by the method described in Example 185(d) from 4-((6S, 2R)-2,6-dimethylpiperidyl)-6-[2-(4-fluorophenyl)ethynyl]-2-methylpyrimidine-5-ylamine (Example 186(a)) (335 mg,
25 0.99 mmol, 1.0 eq). The free base of the product was obtained as a brown solid (175 mg, 53%). Mp: 210-203

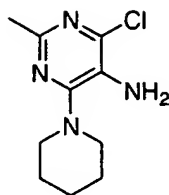
°C. ¹H NMR (CDCl₃, 400 MHz): d 1.27 (d, 6, J = 6.8), 1.66-1.69 (m, 3), 1.81-1.96 (m, 3), 2.61 (s, 3), 4.61 (br s, 2), 6.71 (s, 1), 7.17 (t, 1, J = 8.5), 7.63 (dd, 2, J = 5.2, 8.5), 8.32 (s, 1). MS m/z: 339 (M+H). The
5 above material (175 mg, 0.52 mmol, 1.0 eq) was used to prepare HCl salt by the method described in 185(d) to 86 mg (49%) of the title compound as a brown solid.
Mp: >275 °C. ¹H NMR (DMSO-d₆, 400 MHz): d 1.34 (d, 6, J = 6.7), 1.59 (m, 1), 1.78 (m, 4), 1.94 (m, 1), 2.61
10 (s, 3), 14 (br s, 2), 6.88 (s, 1), 7.51-7.59 (m, 3), 7.95 (d, 2, J = 6.8), 11.60 (s, 1), 14.28 (s, 1). MS m/z: 339 (M+H), m/z: 337 (M-H). Anal. Calcd for C₂₀H₂₃FN₄·HCl·H₂O: C, 61.14; H, 6.67; N, 14.26. Found: C, 61.05; H, 6.78; N, 14.18.

15

**Example 187****(a) 6-Chloro-2-methyl-5-nitro-4-piperidylpyrimidine.**

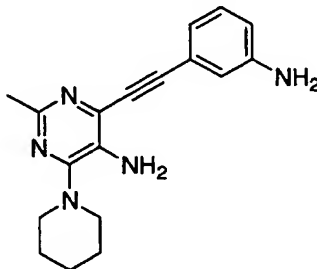
To a solution of 4,6-dichloro-2-methyl-5-nitro
20 pyrimidine (Example 76(b)) (8.00 g, 38.6 mmol, 1.00 eq) in THF (60 mL) was added a solution of piperidine (Aldrich Chemical Company, 3.29 g, 38.6 mmol, 1.00 eq) and diisopropylethylamine (Aldrich Chemical Company, 5.09 g, 39.4 mmol, 1.02 eq) dropwise through a
25 additional funnel under N₂ at room temperature for 3 days. Diisopropylethylamine hydrogen chloride was filtered away as white solid, and the organic layer was concentrated in vacuo. The crude material was purified by flash chromatography on silica gel with 0-8%
30 EtOAc/hexanes as eluant to afford the title compound (8.63 g, 87%) as a yellow solid. Mp: 62-64 °C. ¹H NMR (CDCl₃, 400 MHz): d 1.67 (m, 6), 2.50 (s, 3), 2.53 (m, 4).

290



(b) 6-Chloro-2-methyl-4-piperidylpyrimidine-5-ylamine.

A solution of 6-chloro-2-methyl-5-nitro-4-piperidylpyrimidine (4.06 g, 15.8 mmol, 1.0 eq) in MeOH
 5 (68 mL) was hydrogenated in the presence of PtO₂ (Aldrich Chemical Company, 179 mg, 0.79 mmol, 0.05 eq) under H₂ (60 psi) at room temperature for 5 h. The reaction mixture was passed through a pad of Celite® and concentrated in vacuo. The crude material was
 10 purified by flash chromatography on silica gel with 0-15% EtOAc/hexanes as eluant to afford the title compound (1.86 g, 52%) as a orange oil. ¹H NMR (CDCl₃, 400 MHz): d 1.67 (m, 6), 2.48 (s, 3), 3.25 (m, 4), 3.67 (br s, 2). MS m/z: 227 (M+H).



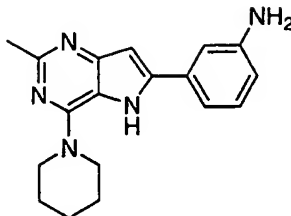
15

(c) 6-[2-(3-Aminophenyl)ethynyl]-2-methyl-4-piperidylpyrimidine-5-ylamine.

This compound was synthesized by the method described in example 1(c) from 6-chloro-2-methyl-4-piperidylpyrimidine-5-ylamine (Example 187(b)) (1.42
 20 g, 6.26 mmol, 1.0 eq) and 3-ethynylaniline (TCI America, 1.47 g, 12.5 mmol, 2.0 eq). The title compound was obtained as a red solid (625 mg, 33%). ¹H NMR (CDCl₃, 400 MHz): d 1.69 (m, 6), 2.52 (s, 3), 3.27
 25 (m, 4), 3.71 (s, 2), 3.92 (s, 2), 6.70 (d, 1, J =

291

7.8), 6.90 (s, 1), 6.99 (d, 1, $J = 7.8$) 7.14 (t, 1, $J = 7.8$). MS m/z : 308 (M+H).

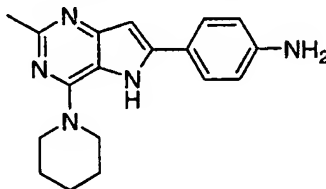


(d) 3-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenylamine Hydrochloride Monohydrate.

This compound was synthesized by the method described in Example 185(d) from 6-[2-(3-aminophenyl)ethynyl]-2-methyl-4-piperidylpyrimidine-5-ylamine (Example 187(c)) (492 mg, 1.6 mmol, 1.0 eq). The free base of the product was obtained as an off-white solid (202 mg, 34%). ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.64 (br s, 6), 2.41 (s, 3), 3.72 (br s, 4), 5.21 (br s, 2), 6.53 (s, 1), 6.60 (d, 1, $J = 7.6$), 7.00 (m, 2), 7.12 (t, 1, $J = 7.6$), 10.97 (s, 1). MS m/z : 308 (M+H), m/z : 306 (M-H). The above material (202 mg, 0.66 mmol, 1.0 eq) was used to prepare HCl salt by the method described in Example 185(d) to give 80 mg (35%) of the title compound as a brown solid. Mp: $>275^\circ\text{C}$. ^1H NMR (DMSO- d_6 , 400 MHz): δ 1.70 (m, 6), 2.56 (s, 3), 4.04 (m, 4), 5.41 (br s, 2), 6.71 (m, 2), 7.03 (m, 2), 7.19 (m, 1), 11.95 (s, 1), 14.25 (s, 1). MS m/z : 308 (M+H), m/z : 306 (M-H). Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_5 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 59.74; H, 6.69; N, 19.36. Found: C, 59.79; H, 6.58; N, 19.34.

25

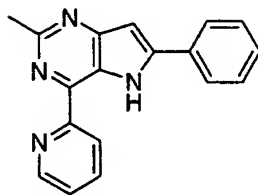
Example 188



**4-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)
phenylamine Hydrochloride.**

A solution of 6-chloro-2-methyl-4-piperidyl
pyrimidine-5-ylamine (Example 187(a)) (1.36 g, 6.0
5 mmol, 1.0 eq), $\text{Pd}_2(\text{PPh}_3)_2\text{Cl}_2$ (Aldrich Chemical Company,
210 mmg, 0.30 mmol, 0.05 eq), Cu(I)I (Aldrich Chemical
Company, 57 mg, 0.30 mmol, 0.05 eq) in triethylamine
(10 mL) was deoxygenated by bubbling N_2 for 10 min, and
was heated to 70 °C. A solution of 4-ethynylaniline
10 (Lavastre, O; Cabioch, S.; Dixneuf, P. H. and Vohlidal,
J. *Tetrahedron*, 1997, 53, 7595. 1.05 g, 9.0 mmol, 1.5
eq) in triethylamine (10 mL) deoxygenated by bubbling
 N_2 was transferred through a canula needle slowly. The
final reaction mixture was stirred under N_2 at 70 °C for
15 48 h. Upon cooling to the room temperature, the
reaction was diluted with CH_2Cl_2 (20 mL) and MeOH (20
mL), passed through a pad of Celite® and concentrated
in vacuo. The crude material was purified by flash
chromatography on silica gel with 10% DMF-0.5%
20 Triethylamine-Toluene as eluant to afford the free base
of the product (370 mg, 20%) as an orange solid. Mp:
239-242 °C. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 1.63 (br s,
6), 2.39 (s, 3), 3.65 (br s, 4), 5.42 (s, 2), 6.46 (s,
1), 6.46 (s, 1), 6.64 (d, 2, $J = 8.5$), 7.56 (d, 2, $J =$
25 8.5), 10.65 (s, 1). MS m/z : 308 (M+H). The above
material (107 mg, 0.35 mmol, 1.0 eq) was used to
prepare HCl salt by the method described in 1 (d) to
give 47 mg (40%) of the title compound as a brown
solid. Mp: >280 °C. ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 1.68
30 (m, 6), 2.54 (s, 3), 4.00 (m, 4), 5.70 (br s, 2), 6.63
(s, 1), 6.67 (d, 2, $J = 8.5$), 7.64 (d, 2, $J = 8.5$),
11.55 (s, 1), 13.97 (s, 1). MS m/z : 308 (M+H), m/z :
306 (M-H). Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_5 \cdot \text{HCl}$: C, 62.87; H,
6.45; Cl, 10.31 ; N, 20.37. Found: C, 62.66; H, 6.35;
35 Cl, 10.56 ; N, 20.17.

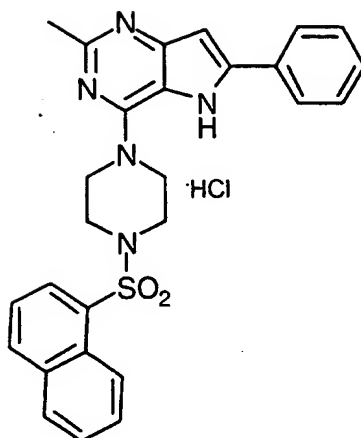
Example 189



**2-Methyl-6-phenyl-4-(2-pyridyl)pyrrolo[3,2-d]
pyrimidine.**

- 5 A mixture of 4-chloro-2-methyl-6-phenylpyrrolo
[3,2-d]pyridine (150 mg, 0.61 mmol), 2-Pyridinyl
tributylstannane (Maybridge, 270 mg, 0.73 mmol, 1.2
eq), tris(dibenzylideneacetone)dipalladium (0) (Aldrich
10 Chemical Company, 14 mg, 0.015 mmol, 0.025 eq) and
triphenylphosphine (Aldrich Chemical Company, 32 mg,
0.12 mmol, 0.2 eq) in anhydrous toluene was refluxed
under N₂ for 48 h. Upon cooling to the room
temperature, the reaction mixture was quenched with 5%
15 HCl (30 mL), then neutralized with Na₂CO₃. The crude
product was extracted with CHCl₃ (60 mL x 3), washed
with water (150 mL x 1), saturated NaCl (150 mL x 1),
dried with Na₂SO₄ and concentrated *in vacuo*.
Chromatography (silica gel, 0-0.5% MeOH/CH₂Cl₂) afforded
20 155 mg (yellow solid, 89%). Mp: 182-183 °C. ¹H NMR
(CDCl₃, 400 MHz): d 2.90 (s, 3), 6.92 (d, 1, *J* = 2.4),
7.4-7.5 (m, 2), 7.55 (t, 2, *J* = 7.3), 7.67 (m, 1), 7.84
(d, 2, *J* = 7.3), 7.94 (t, 1, *J* = 7.9), 8.77 (d, 1, *J* =
7.9), 8.82 (d, 1, *J* = 4.2), 10. 96 (s, 1). MS *m/z*:
25 287 (M+1), 285 (M-1).

294

**Example 190****1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-4-naphthylsulfonyl piperazine Hydrochloride Hydrate.**

5 To an oven-dried, 50 ml round-bottomed flask was added 2-methyl-6-phenyl-4-piperazinylpyrrolo[3,2-d]pyrimidine (Example 26) (250 mg, 0.85 mmol), 1-naphthalenesulfonyl chloride (Aldrich Chemical Company) (232 mg, 1.02 mmol) and CH₂Cl₂ (25 ml). The slurry was

10 stirred at room temperature under an N₂ as triethylamine (142 mL, 1.02 mmol) was added dropwise over 2 min. After 6 h the reaction was washed with saturated NaHCO₃ (3 x 20 ml) and then the aqueous layers were back extracted with CH₂Cl₂ (3 x 10 ml). The

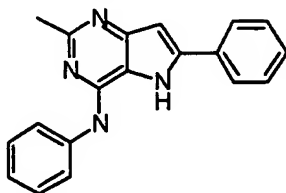
15 organic layers were combined, dried with MgSO₄, filtered and concentrated in vacuo to leave a solid. The white solid was dried under vacuum overnight to give 391 mg (95%) of the free base of the title compound. The free base (391 mg, 0.80 mmol) was

20 dissolved in a mixture of hot CH₂Cl₂/EtOAc (20ml) and anhydrous ethereal HCl (0.80 mL of a 1 M soln, 0.80 mmol) was added dropwise forming a precipitate immediately. After stirring at room temperature for 12

25 h the solution was filtered, solids collected, and dried in a vacuum oven at 60 °C overnight to give a quantitative yield of the title compound as light

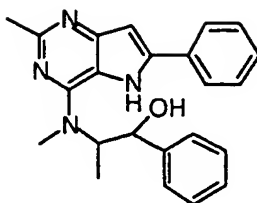
yellow solid. Mp: 195 °C (dec). ¹H NMR (DMSO-*d*₆; 400 MHz): δ 2.53 (s, 4), 4.11 (t, 4, *J* = 4.7), 6.89 (s, 1), 7.53 (m, 3), 7.71 (m, 3), 7.94 (dd, 2, *J* = 6.6, *J* = 1.4), 8.11 (d, 1, *J* = 8.0), 8.20 (dd, 1, *J* = 6.6, *J* = 0.6), 8.31 (d, 1, *J* = 8.2), 8.72 (d, 1, *J* = 8.6), 12.03 (s, 1). MS *m/z*: 484.5 (M+1). Anal. Calcd for C₂₇H₂₅N₅O₂S·HCl·2H₂O: C, 58.53; H, 5.09; N, 12.64; Cl, 6.40. Found: C, 58.45; H, 5.28; N, 12.49; Cl, 6.51.

10

Example 191**(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl) phenylamine Hydrochloride.**

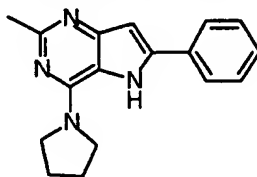
To a 5-mL, vial were added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (Example 1(e)) (100 mg, 0.41 mmol) and aniline (Aldrich Chemical Company) (0.37 mL, 4.1 mmol), followed by EtOH (1.5 mL). The reaction was heated at reflux for 4 h. The reaction mixture was allowed to cool to room temperature and the precipitate was collected by filtration, washed with hexanes, dried in a vacuum oven overnight to give 114 mg of a brown solid. The material was recrystallized from EtOH to give 57 mg (41%) of the title compound as an off-white solid. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 2.67 (s, 3), 7.04 (s, 1), 7.21-7.23 (m, 1), 7.44-7.59 (m, 5), 8.03 (d, 2, *J* = 8.0), 8.15 (d, 2, *J* = 8.0), 11.61 (br s, 1), 13.84 (br s, 1). MS *m/z*: 301 (M+1).

296

**Example 192**

2-[Methyl(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amino]-1-phenylpropan-1-ol.

5 To a 5-mL, Wheaton vial were added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (100 mg, 0.41 mmol) and ephedrine hydrochloride (Aldrich Chemical Company) (410 mg, 2.1 mmol), followed by addition of a solution of potassium carbonate (0.71
10 g, 5.1 mmol) in water (2.5 mL). The reaction mixture was stirred at 120 °C for 20 h, allowed to cool to room temperature and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄, concentrated in vacuo to give a brown residue, which was purified by flash
15 chromatography on silica gel with 1:1 EtOAc/hexanes as eluant to give 23 mg (15%) of the title compound as a tan solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.21 (d, 3, J = 6.8), 2.42 (s, 3), 3.21 (s, 3), 4.91 (m, 1), 5.02 (m, 1), 5.87 (br s, 1), 6.69 (s, 1), 7.18-7.85 (m, 10),
20 10.73 (br s, 1). MS m/z: 373 (M+1), 371 (M-1).

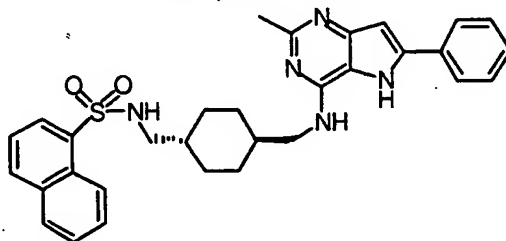
Example 193

2-Methyl-6-phenyl-4-pyrrolidinylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

25 This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (500

mg, 2.1 mmol), pyrrolidine (Aldrich Chemical Company) (0.86 mL, 10.3 mmol), and K_2CO_3 (2.83 g, 20.5 mmol) in H_2O (10 mL) to give 0.722 g of the free base as an off-white solid. To a solution of the above material in
 5 $CHCl_3$ (10 mL) and MeOH (0.5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (2.0 mL, 2.0 mmol). After stirring the reaction at room temperature for 40 min, the precipitate formed was collected by filtration, recrystallized in MeOH/ H_2O to give 0.37 g
 10 (57%) of the title compound as off-white crystals. Mp: $>296^\circ C$. 1H NMR ($DMSO-d_6$; 400 MHz): δ 1.99–2.08 (m, 4), 2.57 (s, 3), 3.81 (m, 2), 4.18 (m, 2), 6.88 (s, 1), 7.49–7.57 (m, 3), 7.96 (d, 2, $J = 6.9$), 11.62 (br s, 1). MS m/z : 279 ($M+1$). Anal. Calcd for $C_{17}H_{18}N_4 \cdot HCl \cdot H_2O$:
 15 C, 61.35; H, 6.36; N, 16.83; Cl, 10.65. Found: C, 61.55; H, 6.49; N, 16.75; Cl, 10.56.

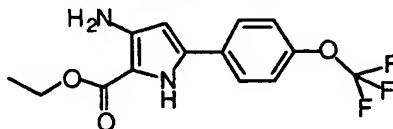
Example 194



20 **trans-[(4-[(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)amino]methyl)cyclohexyl)methyl](naphthylsulfonyl)amine Hydrochloride Hydrate.**

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-
 25 6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (300 mg, 1.2 mmol), trans-[(4-(aminomethyl)cyclohexyl)methyl](naphthylsulfonyl)amine (Rueger, H. et al WO 97/20823) (2.0 g, 6.1 mmol), and K_2CO_3 (1.7 g, 12.3 mmol) in H_2O (8 mL). The residue was purified by flash
 30 chromatography on silica gel with 100:5 $CHCl_3$ /MeOH as

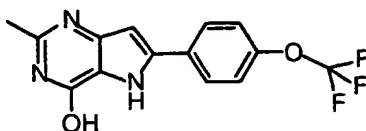
eluant to give 473 mg (71%) of the free base as an off-white solid. To a solution of the above material in MeOH (5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.9 mL, 0.9 mmol). After stirring the
5 reaction at room temperature for 30 min, the precipitate formed was collected by filtration, recrystallized in MeOH/H₂O to give 0.19 g of the title compound as off-white crystals. Mp: 165-170 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 0.71-0.88 (m, 4), 1.25 (m, 1),
10 1.53 (m, 1), 1.63-1.66 (m, 2), 1.76-1.78 (m, 2), 2.57 (s, 3), 2.63 (m, 2), 3.46 (m, 2), 6.93 (s, 1), 7.47-8.22 (m, 12), 8.68 (br s, 1), 9.28 (br s, 1), 13.23 (br s, 1), 14.04 (br s, 1). MS *m/z*: 540 (M+1). Anal. Calcd for C₃₁H₃₃N₅O₂S•HCl•2H₂O: C, 60.82; H, 6.26; N,
15 11.44; Cl, 5.79; S, 5.24. Found: C, 60.73; H, 6.16; N, 11.35; Cl, 5.91; S, 5.16.

Example 195

20 **(a) Ethyl 3-amino-5-[4-(trifluoromethoxy)phenyl]pyrrole-2-carboxylate.**

To a 250-mL, round-bottomed flask were added 4-trifluoromethoxybenzoyl acetonitrile (5.00 g, 21.8 mmol), *p*-toluenesulfonic anhydride (8.55 g, 26.2 mmol)
25 and CH₂Cl₂ (100 mL). To the above solution was then added Et₃N (4.6 mL, 32.7 mmol) dropwise. After 16 h of stirring at ambient temperature, the reaction mixture was partitioned between H₂O and CH₂Cl₂. The organic layer was separated, and the aqueous layer was
30 extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give an orange solid. Sodium ethoxide was prepared freshly from Na^o (1.76 g, 76.3 mmol) and absolute ethanol (50

mL) in an oven-dried, 250-mL, round-bottomed flask equipped with a positive flow of N₂ gas. To the above solution was then added a solution of the crude orange solid and diethyl aminomalonate hydrochloride (5.54 g, 26.2 mmol) in ethanol (85 mL) and THF (7 mL) dropwise through an addition funnel. After the addition was completed, the reaction mixture was stirred at ambient temperature for 3 h and concentrated in vacuo. Water and EtOAc were added, and the aqueous layer was back extracted with EtOAc (3x). The combined EtOAc layers were dried over Na₂SO₄ and concentrated in vacuo to give a dark-red solid. This material was purified by flash chromatography on silica gel with 1:9 EtOAc/hexanes as eluant to give 2.58 g (38%) of the title compound as an off-white solid. Mp: 175.0-178.0 °C. ¹H NMR (DMSO-d₆; 500 MHz) δ 1.30 (t, 3H, J = 7.0), 4.24 (q, 2H, J = 7.0), 5.12 (br s, 2H), 6.04 (d, 1H, J = 2.3), 7.35 (d, 2H, J = 8.6), 7.88 (d, 2H, J = 8.6), 10.86 (br s, 1H); MS m/z: 314 (M+1); IR (Nujol, cm⁻¹): 3446, 3313, 1669; Anal. Calcd for C₁₄H₁₃F₃N₂O₃: C, 53.51; H, 4.17; N, 8.91. Found: C, 53.24; H, 4.28; N, 8.81.

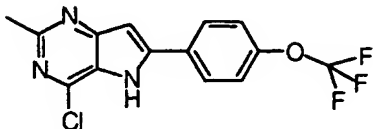


(b) 2-Methyl-6-[4-(trifluoromethoxy)phenyl]pyrrolo[3,2-d]pyrimidin-4-ol.

This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-[4-(trifluoromethoxy)phenyl]pyrrole-2-carboxylate (Example 195(a)) (2.24 g, 7.1 mmol), dry HCl gas in acetonitrile (60 mL) and then 6% aqueous sodium hydroxide (30 mL) and ethanol (50 mL) to give 1.68 g (76%) of the title compound as off-white solid. ¹H NMR (DMSO-d₆; 500 MHz): δ 2.31 (s, 3), 6.81 (s, 1), 7.43

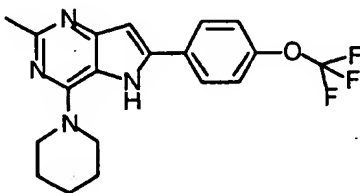
300

(d, 2, $J = 8.6$), 8.05 (d, 2, $J = 8.6$), 11.81 (br s, 1), 12.36 (br s, 1). MS m/z : 310 ($M+1$), 308 ($M-1$).



5 **(c) [4-(4-Chloro-2-methylpyrrolo[4,5-d]pyrimidin-6-yl)phenoxy]trifluoromethane.**

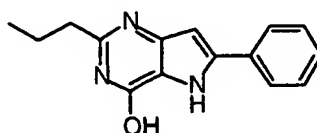
This compound was prepared according to the method described in Example 68 (b) by employing 2-methyl-6-[4-(trifluoromethoxy)phenyl]pyrrolo[3,2-d]pyrimidin-4-ol (Example 195(b)) (1.67 g, 5.4 mmol) and POCl_3 (12.6 mL, 135 mmol) to give 1.32 g (75%) of the title compound as brown solid. ^1H NMR (CDCl_3 ; 500 MHz): d 2.80 (s, 3), 6.93 (s, 1), 7.38 (d, 2, $J = 8.5$), 7.80 (d, 2, $J = 8.5$). MS m/z : 328, 330 ($M+1$); 326, 328 ($M-1$).



15 **(d) Trifluoro[4-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenoxy]methane Hydrochloride Monohydrate.**

This compound was prepared according to the method described in Example 2 by employing [4-(4-chloro-2-methylpyrrolo[4,5-d]pyrimidin-6-yl)phenoxy]trifluoro methane (Example 195(c)) (650 mg, 2.0 mmol), piperidine (Aldrich Chemical Company) (1.0 mL, 9.9 mmol), and K_2CO_3 (2.7 g, 20 mmol) in H_2O (15 mL) to give 351 mg (47%) of the free base as a tan solid. To a solution of the above material in CHCl_3 (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.0 mL, 1.0 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in *vacuo* and the solid obtained was recrystallized in $\text{MeOH}/\text{H}_2\text{O}$ to give 0.156 g

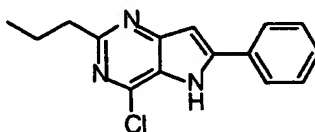
of the title compound as off-white crystals. ^1H NMR (DMSO- d_6 ; 500 MHz): δ 1.70-1.72 (m, 6), 2.57 (s, 3), 4.06-4.07 (m, 4), 6.93 (s, 1), 7.56 (d, 2, $J = 8.6$), 8.13 (d, 2, $J = 8.6$), 12.01 (br s, 1), 14.21 (br s, 1).
5 MS m/z : 377 (M+1). Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_4\text{O} \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 52.97; H, 5.15; N, 13.00; Cl, 8.23. Found: C, 53.01; H, 5.13; N, 12.90; Cl, 8.34.

Example 196

10

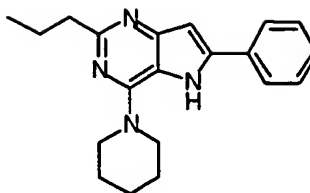
(a) 6-Phenyl-2-propylpyrrolo[3,2-d]pyrimidin-4-ol.

This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-phenylpyrrole-2-carboxylate (Example 66(b)) (2.05 g,
15 8.9 mmol), dry HCl gas in butyronitrile (70 mL) and then 6% aqueous sodium hydroxide (30 mL) and ethanol (50 mL) to give 2.12 g (94%) of the title compound as a gray solid. ^1H NMR (DMSO- d_6 ; 400 MHz): δ 0.92 (t, 3, $J = 7.4$), 1.67-1.77 (m, 2), 2.55 (t, 2, $J = 7.4$), 6.80
20 (s, 1), 7.32-7.46 (m, 3), 7.93 (d, 2, $J = 7.6$), 11.77 (br s, 1), 12.29 (br s, 1). MS m/z : 254 (M+1).

**(b) 4-Chloro-6-phenyl-2-propylpyrrolo[3,2-d]pyrimidine.**

This compound was prepared according to the method described in Example 68 (b) by employing 6-phenyl-2-propylpyrrolo[3,2-d]pyrimidin-4-ol (Example 196(a)) (2.12 g, 8.4 mmol) and POCl_3 (15.7 mL, 168 mmol) to give 1.46 g (64%) of the title compound as a tan solid.
25 ^1H NMR (CDCl_3 ; 500 MHz): δ 1.01 (t, 3, $J = 7.4$), 1.85-1.94 (m, 2), 2.99 (t, 2, $J = 7.7$), 6.95 (s, 1), 7.45-7.53 (m, 3), 7.76 (d, 2, $J = 7.9$), 8.95 (br s, 1).
30

302

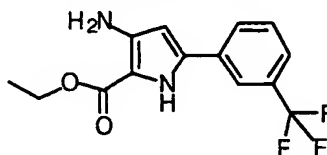


(c) 6-Phenyl-4-piperidyl-2-propylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-6-phenyl-2-propylpyrrolo[3,2-d]pyrimidine (Example 196 (b)) (500 mg, 1.8 mmol), piperidine (Aldrich Chemical Company) (0.91 mL, 9.2 mmol), and K_2CO_3 (2.54 g, 18 mmol) in H_2O (15 mL) to give 534 mg (91%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.7 mL, 1.7 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/ H_2O to give 0.324 g of the title compound as off-white crystals. Mp: 258.0-262.5 °C. 1H NMR ($DMSO-d_6$; 400 MHz): δ 0.92 (t, 3, $J = 7.4$), 1.67 (m, 6), 1.72-1.81 (m, 2), 2.77 (t, 2, $J = 7.4$), 4.02-4.03 (m, 4), 6.86 (s, 1), 7.45-7.53 (m, 3), 7.91 (d, 2, $J = 7.0$), 12.00 (br s, 1). MS m/z : 321 ($M+1$). Anal. Calcd for $C_{20}H_{24}N_4 \cdot HCl \cdot H_2O$: C, 64.07; H, 7.26; N, 14.96; Cl, 9.46. Found: C, 64.16; H, 7.31; N, 15.01; Cl, 9.57.

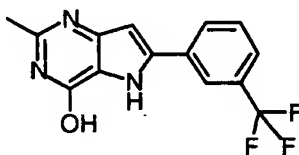
25

Example 197



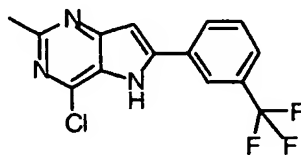
(a) Ethyl 3-amino-5-[3-(trifluoromethyl)phenyl]pyrrole-2-carboxylate.

This compound (5.22 g, 37%) was prepared according to the method described in Example 195(a) by employing 3-trifluoromethylbenzoyl acetonitrile (10 g, 46.9 mmol) and was recrystallized from toluene. Mp: 181.5-182.0 °C. ¹H NMR (DMSO-*d*₆; 500 MHz) δ 1.31 (t, 3H, *J* = 7.0), 4.25 (q, 2H, *J* = 7.0), 5.12 (br s, 2H), 6.15 (d, 1H, *J* = 2.6), 7.58 (d, 2H, *J* = 8.1), 8.00-8.01 (m, 1H), 8.22 (s, 1H), 11.06 (br s, 1H); MS *m/z*: 298 (M+1); IR (Nujol, cm⁻¹): 3441, 3356, 1641; Anal. Calcd for C₁₄H₁₃F₃N₂O₂: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.10; H, 4.48; N, 9.14.



(b) 2-Methyl-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidin-4-ol.

This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-[3-(trifluoromethyl)phenyl]pyrrole-2-carboxylate (Example 197(a)) (5.05 g, 17.0 mmol), dry HCl gas in acetonitrile (120 mL) and then 6% aqueous sodium hydroxide (70 mL) and ethanol (120 mL) to give 2.82 g (57%) of the title compound as an off-white solid. ¹H NMR (DMSO-*d*₆; 500 MHz): δ 2.32 (s, 3), 6.94 (s, 1), 7.65-7.67 (m, 2), 8.21-8.22 (m, 1), 8.37 (s, 1), 11.83 (br s, 1), 12.50 (br s, 1). MS *m/z*: 294 (M+1).

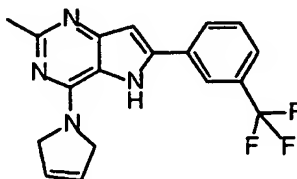


(c) 4-Chloro-2-methyl-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidine.

This compound was prepared according to the method described in Example 68 (b) by employing 2-methyl-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidin-4-ol

304

(Example 197(b)) (2.82 g, 9.6 mmol) and POCl₃ (18 mL, 192 mmol) to give 1.33 g (45%) of the title compound as a tan solid. ¹H NMR (CDCl₃; 400 MHz): δ 2.79 (s, 3), 6.99 (s, 1), 7.63-7.73 (m, 2), 8.14 (d, 1, *J* = 7.6), 8.40 (s, 1).



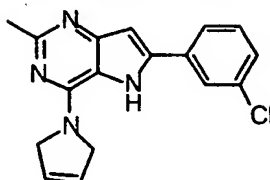
(d) 2-Methyl-4-(3-pyrrolinyl)-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

10 This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-[3-(trifluoromethyl)phenyl]pyrrolo[3,2-d]pyrimidine (Example 197(c)) (400 mg, 1.3 mmol), 3-pyrroline (Aldrich Chemical Company) (0.49 mL, 6.4 mmol), and

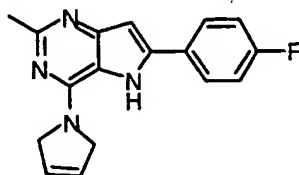
15 K₂CO₃ (1.78 g, 12.8 mmol) in H₂O (10 mL) to give 422 mg (96%) of the free base as a tan solid. To a solution of the above material in CHCl₃ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.3 mL, 1.3 mmol). After stirring the reaction at room temperature

20 for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/H₂O to give 0.226 g of the title compound as off-white crystals. Mp: >270 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 2.61 (s, 3), 4.61 (m, 2), 5.06 (m, 2), 6.16 (d, 2, *J* = 18), 7.11 (s, 1), 7.79-7.83 (m, 1), 7.89 (d, 1, *J* = 7.9), 8.29 (d, 1, *J* = 7.9), 8.35 (s, 1), 11.74 (br s, 1). MS *m/z*: 345 (M+1). Anal. Calcd for C₁₈H₁₇F₃N₄•HCl•H₂O: C, 54.21; H, 4.55; N, 14.05; Cl, 8.89. Found: C, 54.21; H, 4.39; N, 13.80; Cl, 8.75.

305

Example 198**6-(3-Chlorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo
[3,2-d]pyrimidine Hydrochloride Hydrate.**

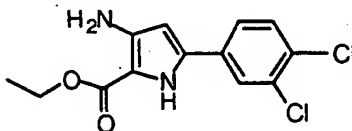
5 This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-(3-chlorophenyl)pyrrolo[3,2-d]pyrimidine (Example (70(d)) (474 mg, 1.7 mmol), 3-pyrroline (Aldrich Chemical Company) (0.65 mL, 8.5 mmol), and K₂CO₃ (2.35 g, 17 mmol) in H₂O (10 mL) to give the free base as a tan solid. To a solution of the above material in CHCl₃ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.7 mL, 1.7 mmol). After stirring the reaction at room temperature for 30 min, the
15 solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/H₂O to give 0.317 g (54%) of the title compound as off-white crystals. Mp: 287.5-293.0 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 2.60 (s, 3), 4.60 (m, 2), 5.06 (m, 2), 6.14 (d, 2, J = 14), 7.04 (s, 1); 7.57-7.60 (m, 2), 7.95-7.98 (m, 1), 8.13 (s, 1),
20 11.64 (br s, 1). MS m/z: 311 (M+1). Anal. Calcd for C₁₇H₁₅ClN₄•HCl•1.25H₂O: C, 55.24; H, 5.04; N, 15.16; Cl, 19.18. Found: C, 55.24; H, 4.92; N, 15.02; Cl, 18.98.



25

Example 199**6-(4-Fluorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo
[3,2-d]pyrimidine Hydrochloride Hydrate.**

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-(4-fluorophenyl)pyrrolo[3,2-d]pyrimidine (example 73(c)) (413 mg, 1.6 mmol), 3-pyrroline (Aldrich Chemical Company) (0.61 mL, 7.9 mmol), and K_2CO_3 2.18 g, 15.8 mmol) in H_2O (10 mL) to give the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.6 mL, 1.6 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/ H_2O to give 0.334 g (64%) of the title compound as tan crystals. 1H NMR ($DMSO-d_6$; 400 MHz): d 2.60 (s, 3), 4.58 (m, 2), 5.05 (m, 2), 6.13 (d, 2, $J = 12$), 6.92 (s, 1), 7.37-7.44 (m, 2), 8.03-8.09 (m, 2), 11.65 (br s, 1). MS m/z : 295 (M+1). Anal. Calcd for $C_{17}H_{15}FN_4 \cdot HCl \cdot 1.25H_2O$: C, 57.82; H, 5.27; N, 15.87; Cl, 10.04. Found: C, 57.82; H, 5.29; N, 15.71; Cl, 9.94.



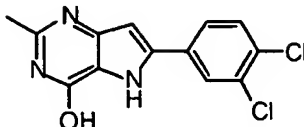
Example 200

(a) Ethyl 3-amino-5-(3,4-dichlorophenyl)pyrrole-2-carboxylate.

The title compound (2.43 g, 31%) was prepared according to the method described in Example 195(a) by employing 3,4-dichlorobenzoyl acetonitrile (5.57 g, 26.0 mmol) and was recrystallized from toluene. Mp: 184.0-185.0 °C. 1H NMR ($DMSO-d_6$; 500 MHz) d 1.30 (t, 3H, $J = 7.0$), 4.24 (q, 2H, $J = 7.0$), 5.12 (br s, 2H), 6.11 (s, 1H), 7.60 (d, 1H, $J = 8.5$), 7.72 (d, 1H, $J = 8.5$), 8.14 (s, 1H), 10.95 (br s, 1H); MS m/z : 299 (M+1); IR (Nujol, cm^{-1}): 3440, 3337, 1638; Anal. Calcd

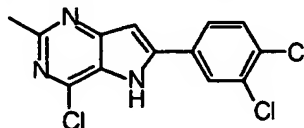
307

for $C_{13}H_{12}Cl_2N_2O_2$: C, 52.19; H, 4.04; N, 9.36; Cl, 23.70.
 Found: C, 52.20; H, 4.12; N, 9.23; Cl, 23.53.



(b) 6-(3,4-Dichlorophenyl)-2-methylpyrrolo[3,2-d]pyrimidin-4-ol.

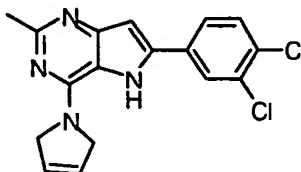
This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-(3,4-dichlorophenyl)pyrrole-2-carboxylate (Example 200(a)) (2.35 g, 7.9 mmol), dry HCl gas in acetonitrile (60 mL) and then 6% aqueous sodium hydroxide (35 mL) and ethanol (60 mL) to give 2.25 g (97%) of the title compound as a tan solid. 1H NMR (DMSO- d_6 ; 500 MHz): δ 2.31 (s, 3), 6.91 (s, 1), 7.69 (d, 1, J = 8.4), 7.91-7.93 (m, 1), 8.27 (s, 1), 11.84 (br s, 1), 12.50 (br s, 1).



15

(c) 6-(3,4-Dichlorophenyl)-4-chloro-2-methylpyrrolo[3,2-d]pyrimidine.

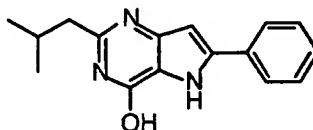
This compound was prepared according to the method described in Example 68 (b) by employing 6-(3,4-dichlorophenyl)-2-methylpyrrolo[3,2-d]pyrimidin-4-ol (Example 200(b)) (2.25 g, 7.7 mmol) and POCl₃ (18 mL, 191 mmol) to give 1.07 g (45%) of the title compound as a tan solid. 1H NMR (CDCl₃; 400 MHz): δ 2.80 (s, 3), 6.93 (s, 1), 7.58 (m, 2), 7.84 (s, 1), 8.71 (br s, 1).



25

(d) 6-(3,4-Dichlorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-methyl-6-(3,4-dichlorophenyl)pyrrolo[3,2-d]pyrimidine (Example 200(c)) (400 mg, 1.3 mmol), 3-pyrroline (Aldrich Chemical Company) (0.49 mL, 6.4 mmol), and K_2CO_3 (1.77 g, 13 mmol) in H_2O (10 mL) to give 381 mg (86%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.1 mL, 1.1 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH to give 0.121 g of the title compound as tan crystals. 1H NMR ($DMSO-d_6$; 400 MHz): d 2.37 (s, 3), 4.37 (m, 2), 4.82 (m, 2), 5.92 (d, 2, $J = 17$), 6.85 (s, 1), 7.62 (d, 1, $J = 8.5$), 7.77-7.79 (m, 1), 8.12 (s, 1), 11.40 (br s, 1). MS m/z : 346 ($M+1$). Anal. Calcd for $C_{17}H_{14}Cl_2N_4 \cdot HCl \cdot 1.75H_2O$: C, 49.39; H, 4.52; N, 13.56; Cl, 25.76. Found: C, 49.39; H, 4.41; N, 13.46; Cl, 25.84.

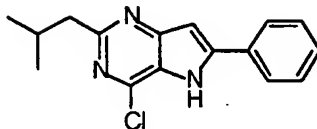


Example 201

(a) 2-(2-Methylpropyl)-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol.

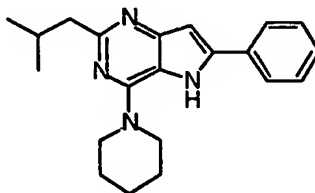
This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-phenylpyrrole-2-carboxylate ((Example 66(b)) (2.50 g, 10.9 mmol), dry HCl gas in isovaleronitrile (50 g) and then 6% aqueous sodium hydroxide (35 mL) and ethanol (50 mL) to give 1.77 g (61%) of the title compound as a brown solid. 1H NMR ($DMSO-d_6$; 500 MHz): d 0.92 (d, 6, $J = 7.0$), 2.13-2.16 (m, 1), 2.44 (d, 2, $J = 7.0$), 6.79

(s,1), 7.32-7.49 (m 3), 7.93 (d, 2, $J = 7.8$), 11.74 (br s,1), 12.28 (br s,1). MS m/z : 268 (M+1), 266 (M-1).



(b) 4-Chloro-2-(2-methylpropyl)-6-phenylpyrrolo[3,2-d]pyrimidine.

This compound was prepared according to the method described in Example 68 (b) by employing 2-(2-methylpropyl)-6-phenylpyrrolo[3,2-d]pyrimidin-4-ol (Example 201(a)) (1.77 g, 6.6 mmol) and POCl₃ (15.5 mL, 165 mmol) to give 0.59 g (31%) of the title compound as a tan solid. ¹H NMR (CDCl₃; 500 MHz): δ 0.99 (d, 6, $J = 6.2$), 2.34 (m, 1), 2.93 (d, 2, $J = 6.2$), 6.99 (s, 1), 7.27-7.42 (m 3), 7.80 (m, 2).



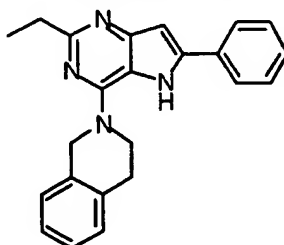
(c) 2-(2-Methylpropyl)-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-(2-methylpropyl)-6-phenylpyrrolo[3,2-d]pyrimidine (Example 201(b)) (588 mg, 2.1 mmol), piperidine (Aldrich Chemical Company) (1.0 mL, 10.3 mmol), and K₂CO₃ (2.85 g, 21 mmol) in H₂O (15 mL) to give the free base as a tan solid. To a solution of the above material in CHCl₃ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (2.0 mL, 2.0 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/H₂O to give 0.313 g (40%) of the title compound as orange crystals. Mp: 226.0-229.5

°C. ¹H NMR (DMSO-d₆; 400 MHz): d 1.19 (d, 6, J = 7.0), 1.93 (m, 6), 2.40-2.50 (m, 1), 2.92 (d, 2, J = 7.0), 4.28-4.30 (m, 4), 7.13 (s, 1), 7.72-7.81 (m, 3), 8.18 (d, 2, J = 8.3), 12.25 (br s, 1). MS m/z: 335.5 (M+1).

5 Anal. Calcd for C₂₁H₂₆N₄•HCl•H₂O: C, 64.85; H, 7.52; N, 14.41. Found: C, 65.12; H, 7.32; N, 14.18.

Example 202

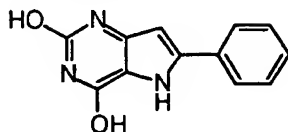


10 2-Ethyl-6-phenyl-4-(2-1,2,3,4-tetrahydroisoquinolyl)pyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.

This compound was prepared according to the method described in Example 2 by employing 2-ethyl-4-chloro-6-phenylpyrrolo[3,2-d]pyrimidine (example (68b)) (500 mg, 1.7 mmol), 1,2,3,4-tetrahydroisoquinoline (Aldrich Chemical Company) (1.1 mL, 8.5 mmol), and K₂CO₃ (2.35 g, 17 mmol) in H₂O (15 mL) to give 410 mg (68%) of the free base as a tan solid. To a solution of the above material in CHCl₃ (10 mL) was added 1N ethereal HCl 20 (Aldrich Chemical Company) (1.2 mL, 1.2 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/H₂O to give 0.42 g of the title compound as tan crystals. Mp: 170.0-171.5 25 °C. ¹H NMR (DMSO-d₆; 500 MHz): d 1.36 (t, 3, J = 7.5), 2.91 (t, 2, J = 7.5), 3.08 (t, 2, J = 5.8), 4.32 (t, 2, J = 5.8), 5.29 (s, 2), 6.92 (s, 1), 7.27-7.41 (m, 4), 7.53-7.60 (m, 3), 8.00 (d, 2, J = 7.3), 11.97 (br s, 1), 14.42 (br s, 1). MS m/z: 355.5 (M+1). Anal. Calcd

311

for $C_{23}H_{22}N_4 \cdot HCl \cdot H_2O$: C, 67.56; H, 6.16; N, 13.70. Found: C, 67.27; H, 6.10; N, 13.47.

Example 203

5

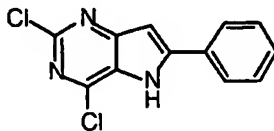
(a) 6-Phenylpyrrolo[3,2-d]pyrimidine-2,4-diol.

In a 1-l round-bottomed flask was added ethyl 3-amino-5-phenylpyrrole-2-carboxylate (Example 66 (b)) (20 g, 87 mmol), followed by acetic acid (435 mL) and H₂O (44 mL). Potassium cyanate (21.2 g, 261 mmol) dissolved in 70 mL of H₂O was then added dropwise through an addition funnel. The reaction mixture was stirred at room temperature for 15 h. The precipitate formed was collected by filtration, washed with H₂O and ether, dried to give a white solid. To the above solid in a 1-L round-bottomed flask was added 6% aqueous sodium hydroxide (435 mL). The suspension was heated at reflux for 2 h. The reaction mixture was acidified using 12 N HCl to pH 6. The precipitate formed was filtered, washed with H₂O, dried in a vacuum oven overnight to give 15.2 g (77%) of the title compound as a white solid. ¹H NMR (DMSO-d₆; 500 MHz): δ 6.29 (s, 1), 7.33-7.43 (m, 3), 7.85 (d, 2, J = 7.3), 10.62 (br s, 1), 10.85 (br s, 1), 12.19 (br s, 1). MS m/z: 226 (M-1).

10

15

20



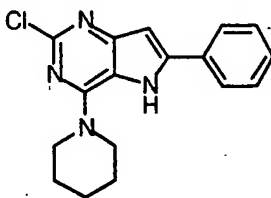
25

(b) 2,4-Dichloro-6-phenylpyrrolo[3,2-d]pyrimidine.

A mixture of 6-phenylpyrrolo[3,2-d]pyrimidine-2,4-diol (Example 203(a)) (6.0 g, 26.6 mmol) and POCl₃ (210 mL, 229 mmol) in a 500-mL, round-bottomed flask was heated at 120 °C for 60 h. POCl₃ was removed in vacuo to give a dark-red residue. Ice-water was added, and

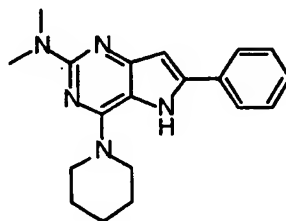
30

the pH of the reaction mixture was adjusted to pH 6 by the addition of aqueous NH_3 at 0 °C. The resulting mixture was extracted three times with EtOAc. Combined organic layer were washed with brine, dried over Na_2SO_4 , concentrated in vacuo and dried in a vacuum oven overnight to give 2.84 g (40%) of the title compound as an orange solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 6.95 (s, 1), 7.50-7.66 (m, 3), 7.77 (d, 2, $J=8.1$), 8.88 (br s, 1).



10 **(c) 2-Chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine.**

This compound was prepared according to the method described in Example 2 by employing 2,4-dichloro-6-phenylpyrrolo[3, 2-d]pyrimidine (Example 203(b)) (2.84 g, 10.8 mmol), piperidine (Aldrich Chemical Company) (5.3 mL, 53.8 mmol), and K_2CO_3 (14.9 g, 108 mmol) in H_2O (100 mL) to give 3.23 g (96%) of the title compound as an orange solid. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.77 (m, 6), 3.83 (m, 4), 6.75 (s, 1), 7.37-7.55 (m, 3), 7.64 (d, 2, $J = 7.3$), 8.21 (br s, 1). MS m/z : 313, 315 (M+1); 311, 313 (M-1).

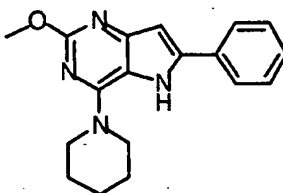


(d) Dimethyl(6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidin-2-yl)amine Hydrochloride Hydrate.

25 A mixture of 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 203(c)) (313 mg, 1 mmol), aqueous dimethylamine (Aldrich Chemical Company) (40

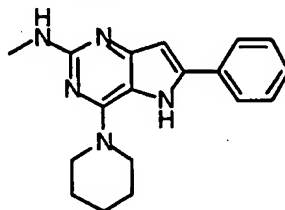
wt. %, 1.5 mL, 12 mmol), 5 mL of *n*-butanol and 0.2 mL of 12 N HCl in a 25-mL, round-bottomed flask was heated at reflux for 32 h under a stream of N₂. After cooling to room temperature, the precipitate was collected by
5 filtration, washed with hexanes and dried in a vacuum oven overnight to give 239 mg (74%) of the title compound as orange crystals. Mp: >300 °C. ¹H NMR (DMSO-*d*₆; 500 MHz): δ 1.68 (m, 6), 3.19 (s, 6), 3.95 (m, 4), 6.70 (s, 1), 7.45–7.54 (m, 3), 7.86 (d, 2, *J* =
10 7.4), 11.58 (br s, 1), 12.22 (br s, 1). MS *m/z*: 322.5 (*M*+1). Anal. Calcd for C₁₉H₂₃N₅•1.2HCl•1.75H₂O: C, 57.68; H, 7.04; N, 17.71; Cl, 10.61. Found: C, 57.68; H, 6.99; N, 17.77; Cl, 10.85.

15

Example 204**2-Methoxy-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Monohydrate.**

A mixture of 2-chloro-6-phenyl-4-piperidylpyrrolo
20 [3,2-*d*]pyrimidine (Example 203(c)) (626 mg, 2 mmol), sodium methoxide (Aldrich Chemical Company) (25 wt. %, 0.78 mL, 4.5 mmol) and 2 mL of DMSO in a 15-mL, round-bottomed flask was heated at reflux for 72 h under a stream of N₂. After cooling to room temperature, the
25 residue was partitioned between H₂O and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂, and the combined CH₂Cl₂ layers were dried over Na₂SO₄, concentrated in vacuo and purified by flash chromatography on silica gel with 1:5 to 1:2 EtOAc/hexanes as eluant to give 217
30 mg (35%) of the free base as a purple solid. To a solution of the above material in CHCl₃ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.75

mL, 0.75 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/H₂O to give 0.117 g of the title compound as a
5 light-green crystals. Mp: 270-276 °C. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.73 (m, 6), 4.05 (m, 7), 6.75 (s, 1), 7.48-7.56 (m, 3), 7.92 (d, 2, *J* = 8.3), 11.87 (br s, 1), 13.87 (br s, 1). MS *m/z*: 309 (M+1). Anal. Calcd for C₁₈H₂₀N₄O•HCl•H₂O: C, 59.58; H, 6.39; N, 15.44; Cl, 9.77. Found: C, 59.59; H, 6.49; N, 15.47; Cl, 9.90.
10

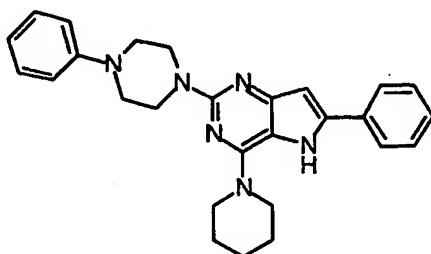
Example 205**Methyl(6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidin-2-yl)amine Hydrochloride Monohydrate.**
15

A mixture of 2-chloro-6-phenyl-4-piperidylpyrrolo [3,2-d]pyrimidine (Example 203(c)) (626 mg, 2 mmol), aqueous methylamine (Aldrich Chemical Company) (40 wt. %, 3.1 mL, 35 mmol), 10 mL of *n*-butanol and 0.4 mL of
20 12 N HCl in a 25-mL, round-bottomed flask was heated at reflux for 48 h under a stream of N₂. After cooling to room temperature, the solvent was evaporated in vacuo and the residue was partitioned between 5% NaHCO₃ and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ and
25 the combined CH₂Cl₂ layers were dried over Na₂SO₄, concentrated in vacuo and purified by flash chromatography on silica gel with 100:2 to 100:5 CHCl₃/MeOH as eluant to give 30 mg (5%) of the free base. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.68 (m, 6), 3.19 (s, 6), 3.95 (m, 4), 6.70 (s, 1), 7.45-7.54 (m, 3),
30 7.86 (d, 2, *J* = 7.4), 11.58 (br s, 1), 12.22 (br s, 1).

315

To a solution of the above material in CHCl_3 (5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.1 mL, 0.1 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/ H_2O to give 15 mg of the title compound as orange crystals. Mp: 195-200 °C. MS m/z : 308.5 (M+1). Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{N}_5 \cdot \text{HCl} \cdot \text{H}_2\text{O}$: C, 59.74; H, 6.68; N, 19.35. Found: C, 59.34; H, 6.69; N, 18.93.

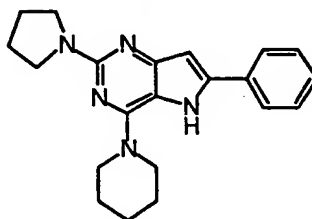
10

Example 206**6-Phenyl-2-(4-phenylpiperazinyl)-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

To the mixture of 2-chloro-6-phenyl-4-piperidyl pyrrolo[3,2-d]pyrimidine (Example 203(c)) (200 mg, 0.64 mmol) and 1-phenylpiperazine (Aldrich Chemical Company) (0.49 mL, 3.2 mmol) in a 50-mL, round-bottomed flask was added a solution of K_2CO_3 (0.89 g, 6.4 mmol) in 10 mL of H_2O . The reaction mixture was heated at reflux for 72 h under a stream of N_2 . After cooling to room temperature, the mixture was partitioned between H_2O and CH_2Cl_2 . The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layers were dried over Na_2SO_4 , concentrated in vacuo and purified by flash chromatography on silica gel with 1:5 to 1:4 EtOAc/hexanes as eluant to give 107 mg (38%) of the free base as white solids. To a solution of the above material in CHCl_3 (5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.24 mL, 0.24 mmol). After

stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the foam obtained was recrystallized in MeOH/H₂O to give 54 mg of the title compound as off-white solids. Mp: 267.5-
5 270.0 °C. MS *m/z*: 439.5 (M+1). ¹H NMR (DMSO-*d*₆; 500 MHz): δ 1.88 (m, 6), 4.07-4.15 (m, 12), 6.89 (s, 1), 7.00-7.02 (m, 2), 7.19 (d, 2, *J* = 8.0), 7.42-7.45 (m, 2), 7.63-7.72 (m, 3), 8.05 (d, 2, *J* = 7.6), 11.81 (br s, 1), 12.73 (br s, 1). Anal. Calcd for
10 C₂₈H₃₂N₆•1.5HCl•1.25H₂O: C, 62.82; H, 6.63; N, 16.28; Cl, 10.51. Found: C, 62.82; H, 6.68; N, 16.26; Cl, 10.63.

Example 207

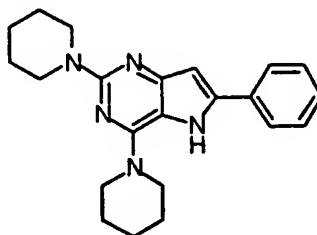


15 6-Phenyl-4-piperidyl-2-pyrrolidinylpyrrolo[3,2-*d*]pyrimidine Hydrochloride Monohydrate.

To the solution of 2-chloro-6-phenyl-4-piperidyl pyrrolo[3,2-*d*]pyrimidine (Example 203(c)) (250 mg, 0.80 mmol) in 2 mL of dioxane in a 5-mL, Wheaton vial was
20 added pyrrolidine (0.33 mL, 4.0 mmol). The vial was capped and heated at 110 °C for 44 h. After cooling to room temperature, the precipitate was collected by filtration, washed with hexanes and dried in air to give 225 mg (81%) of the free base as light-yellow
25 solids. To a solution of the above material in CHCl₃ (5 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.63 mL, 0.63 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the foam obtained was
30 recrystallized in MeOH/H₂O to give 100 mg of the title compound as light-yellow crystals. Mp: >272 °C. ¹H NMR

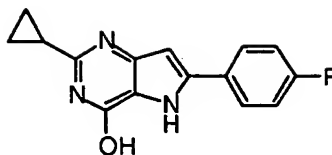
317

(DMSO- d_6 ; 400 MHz): d 1.68-1.70 (m, 6), 2.00 (m, 4), 3.57 (m, 4), 3.96-3.97 (m, 4), 6.67 (s, 1), 7.46-7.56 (m, 3), 7.88 (d, 2, $J = 8.5$), 11.57 (br s, 1), 12.11 (br s, 1). Anal. Calcd for $C_{21}H_{25}N_5 \cdot HCl \cdot H_2O$: C, 62.75; H, 7.02; N, 17.42; Cl, 8.82. Found: C, 62.85; H, 6.93; N, 17.36; Cl, 8.70.

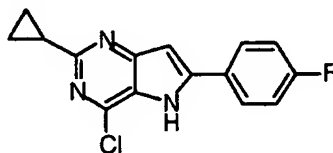
Example 208**10 6-Phenyl-2,4-dipiperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.**

This compound was prepared according to the method described in Example 207 by employing 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 203(c)) (250 mg, 0.8 mmol), piperidine (Aldrich Chemical Company) (0.39 mL, 4.0 mmol) and dioxane (2 mL) to give 198 mg (69%) of the free base as a tan solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (0.54 mL, 0.54 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated in vacuo and the solid obtained was recrystallized in MeOH/ H_2O to give 38 mg of the title compound as light-yellow crystals. Mp: $>272^\circ C$. 1H NMR (DMSO- d_6 ; 400 MHz): d 1.61-1.70 (m, 6), 3.74 (m, 4), 3.94 (m, 4), 6.71 (s, 1), 7.45-7.55 (m, 3), 7.87 (d, 2, $J = 7.3$), 11.61 (br s, 1), 12.44 (br s, 1). Anal. Calcd for $C_{22}H_{27}N_5 \cdot HCl$: C, 66.40; H, 7.09; N, 17.60; Cl, 8.91. Found: C, 66.25; H, 7.21; N, 17.48; Cl, 9.03.

318

**Example 209****(a) 2-Cyclopropyl-6-(4-fluorophenyl)pyrrolo[3,2-d]pyrimidin-4-ol.**

5 This compound was prepared according to the method described in Example 68(a) by employing ethyl 3-amino-5-(4-fluorophenyl)pyrrole-2-carboxylate (Example 73(a)) (1.05 g, 4.2 mmol), dry HCl gas in cyclopropylcyanide (40 g) and then 6% aqueous sodium hydroxide (30 mL) and
10 ethanol (70 mL) to give 1.41 g of the title compound as an off-white solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 0.77-0.83 (m, 4), 1.32 (m, 1), 1.75 (m, 1), 6.54 (s, 1), 7.09-7.14 (m, 2), 7.77-7.81 (m, 2), 11.85 (br s, 1), 12.04 (br s, 1). MS m/z: 270.5 (M+1).

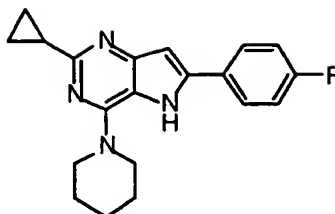


15

(b) 4-Chloro-2-cyclopropyl-6-(4-fluorophenyl)pyrrolo[3,2-d]pyrimidine.

This compound was prepared according to the method described in Example 68 (b) by employing 2-cyclopropyl-6-(4-fluorophenyl)pyrrolo[3,2-d]pyrimidin-4-ol (Example
20 209(a)) (1.14 g, 4.23 mmol), POCl₃ (8 mL, 85 mmol) and benzyltriethylammonium chloride (0.48 g, 2.1 mmol) to give 0.97 g (80%) of the title compound as an orange solid. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.06-1.11 (m, 2),
25 1.18-1.22 (m, 2), 2.31-2.35 (m, 1), 6.83 (s, 1), 7.17-7.22 (m, 2), 7.74-7.77 (m, 2), 9.15 (br s, 1).

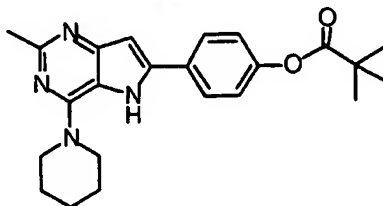
319



(c) 2-Cyclopropyl-6-(4-fluorophenyl)-4-piperidyl pyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.

This compound was prepared according to the method described in Example 2 by employing 4-chloro-2-cyclopropyl-6-(4-fluorophenyl)pyrrolo[3,2-d]pyrimidine (Example 209(b)) (437 mg, 1.5 mmol), piperidine (Aldrich Chemical Company) (0.75 mL, 7.6 mmol), and K_2CO_3 (1.05 g, 7.6 mmol) in H_2O (10 mL) to give 399 mg (78%) of the free base as a beige solid. To a solution of the above material in $CHCl_3$ (10 mL) was added 1N ethereal HCl (Aldrich Chemical Company) (1.2 mL, 1.2 mmol). After stirring the reaction at room temperature for 30 min, the solvent was evaporated *in vacuo* and the solid obtained was recrystallized in MeOH/ H_2O to give 0.14 g of the title compound as off-white crystals. Mp: $>280^\circ C$. 1H NMR ($DMSO-d_6$; 400 MHz): δ 1.34-1.41 (m, 4), 1.88 (m, 6), 2.37-2.41 (m, 1), 4.18 (m, 4), 7.09 (s, 1), 7.62 (t, 2, $J = 8.8$), 8.21-8.25 (m, 2), 12.14 (br s, 1). MS m/z : 337 (M+1). Anal. Calcd for $C_{20}H_{21}FN_4 \cdot HCl \cdot 0.25H_2O$: C, 63.80; H, 6.00; N, 14.88; Cl, 9.42. Found: C, 63.82; H, 5.97; N, 14.91; Cl, 9.70.

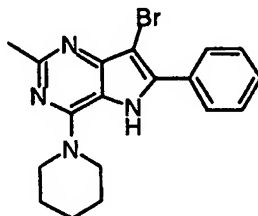
Example 210



4-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl) phenyl 2,2-dimethylpropanoate.

320

To the mixture of 2-methyl-4-piperidyl-6-(4-hydroxyphenyl)pyrrolo[3,2-d]pyrimidine (example 72) (385 mg, 1.25 mmol) and pyridine (5 mL) in a 25-mL, round-bottomed flask was added trimethylacetic anhydride (Aldrich Chemical Company) (0.3 mL, 1.5 mmol). The reaction mixture was heated at reflux for 24 h under a stream of N₂. After cooling to room temperature, the solvent was evaporated *in vacuo* and the residue was partitioned between H₂O and CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ and the combined CH₂Cl₂ layers were dried over Na₂SO₄, concentrated *in vacuo* and purified by flash chromatography on silica gel with 100:2.5 CHCl₃/MeOH as eluant to give 417 mg (85%) of a brown solid. It was recrystallized in EtOH to give 87 mg of the title compound as white solids. Mp: 272-274 °C. MS *m/z*: 393.0 (*M*+1). ¹H NMR (CDCl₃; 400 MHz): δ 1.38 (s, 9), 1.76 (m, 6), 2.60 (s, 3), 3.79 (m, 4), 6.72 (s, 1), 7.17 (d, 2, *J* = 8.6), 7.65 (d, 2, *J* = 8.6), 8.06 (br s, 1). Anal. Calcd for C₂₃H₂₈N₄O₂: C, 70.38; H, 7.19; N, 14.27. Found: C, 70.52; H, 7.20; N, 14.32.

Example 211

25

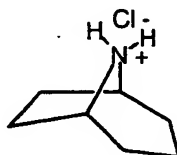
7-Bromo-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine Hydrochloride.

To an oven-dried, 50-mL, round-bottomed flask was added 2-methyl-6-phenyl-4-(piperidinyl)pyrrolo[3,2-d]pyrimidine (Example 35) (500 mg, 1.71 mmol) which was dissolved in glacial AcOH (15 mL). To this

30

321

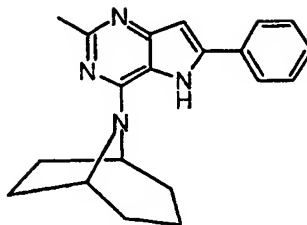
solution was added Br₂ (Aldrich Chemical Company) (90.0 mL, 1.8 mmol) dropwise over 2 min. The resulting dark mixture was diluted with H₂O (10 mL) and the mixture was warmed to 45 °C and stirred for 2 h. The reaction was allowed to cool to room temperature and the crude material was extracted with EtOAc (50 mL) and washed with saturated NaHCO₃ (3 x 50 mL). The organic layer was washed with brine (50 mL), dried over MgSO₄, filtered and evaporated *in vacuo* to give an oily residue. The residue was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant to give 500 mg (79.4% yield) of a yellow solid. Mp: 239-240 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.74 (s, 6), 2.63 (s, 3), 3.83 (s, 4), 7.44 (t, 1, *J* = 2.4), 7.5 (t, 2, *J* = 7.0), 7.80 (d, 2, *J* = 7.1). MS *m/z*: 373.0 (M+1); 369.0, 371.0 (M-1).

**Example 212****(a) 8-Azabicyclo[3.2.1]octane Hydrochloride.**

To an oven-dried, 100-mL, round-bottomed flask was added tropane (2.5 g, 19.96 mmol) followed by toluene (20 mL), and α-chloro-ethyl chloroformate (3.2 mL, 30 mmol). The flask was purged with N₂ and the mixture was heated at 120 °C for 16 h. The reaction was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. The resulting residue was dissolved in MeOH (20 mL) and heated to reflux at 85 °C for 3 h. The solvent was evaporated *in vacuo* and the product dried under vacuum to give 2.90 g (98% yield) of a light brown solid. MS *m/z*: 112.0 (M+1). ¹H NMR

322

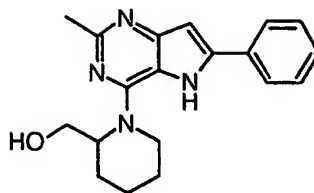
(DMSO- d_6 ; 400 MHz): δ 1.64 (m, 4), 1.95 (m, 6), 3.92 (s, 2), 9.24 (br d, 2, $J = 7.3$).



(b) 4-(8-azabicyclo[3.2.1]oct-8-yl)-2-methyl-6-phenyl pyrrolo[3,2-d]pyrimidine Hydrochloride.

To an oven-dried, 50-mL, round-bottomed flask was added NaOCH₃ (250 mg, 1.03 mmol) and 8-azabicyclo[3.2.1]octane hydrochloride (Example 212(a)) (152 mg, 1.03 mmol) and the resulting mixture was stirred at room temperature for 30 min. To this mixture was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (125 mg, 0.513 mmol) and the mixture was heated to 180 °C for 4 h. The reaction was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant to give 95 mg (60% yield) of light brown solid. The free base (88.0 mg, 0.277 mmol) was dissolved in hot EtOAc (10 mL) and anhydrous ethereal HCl (0.28 mL, of a 1.0 M soln, 0.28 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 65 mg (66% yield) of the title compound as a light brown solid. Mp: >300 °C. ¹H NMR (DMSO- d_6 ; 400 MHz): δ 1.32 (m, 4), 2.63 (s, 3), 3.37 (s, 6), 5.26 (s, 2), 6.94 (s, 1), 7.61 (m, 3), 8.0 (d, $J = 7.0$, 2), 11.84 (s, 1), 14.2 (s, 1). MS m/z : 387.5 (M+1); 385.5 (M-1).

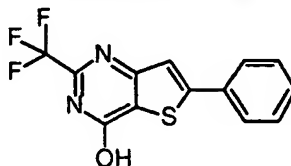
323

**Example 213**

(1-[2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl]-2-piperidyl)methan-1-ol Hydrochloride.

5 To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (250 mg, 1.03 mmol) and 2-hydroxymethyl piperidine (Aldrich Chemical Company) (237 mg, 2.06 mmol). The flask was purged with N₂ and
 10 the mixture was heated to 180 °C for 16 h. The reaction was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with EtOAc as eluant to give 125 mg (38% yield) of an off white solid. ¹H NMR (CDCl₃; 400
 15 MHz); δ 1.74 (m, 6), 2.59 (s, 3), 3.1 (m, 1), 3.8 (m, 1), 4.35 (t, 1, J = 10.9), 4.55 (m, 2), 6.72 (s, 1), 7.44 (m, 3), 7.65 (d, J = 7.3), 9.9 (br, 1). MS m/z: 323.5 (M+1); 321.5 (M-1).

20

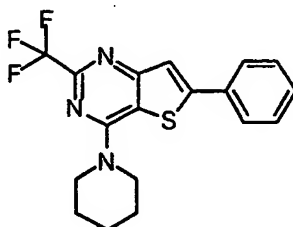
Example 214

(a) 6-Phenyl-2-(trifluoromethyl)thiophene[3,2-d]pyrimidin-4-ol.

To an oven-dried, 100-mL, round-bottomed flask
 25 was added methyl 3-amino-5-phenylthiophene-2-carboxylate (Maybridge Chemical Company) (1.00 g, 4.29 mmol) along with trifluoroacetamide (560 mg, 5 mmol) and the mixture was heated to 190 °C for 16 h. A solid

324

formed in the reaction and as the mixture was allowed to cool to room temperature. Ethanol (50 mL) was added to the reaction mixture and the solid filtered off and dried under vacuum to give 420 mg (33% yield) of a white solid. Mp: 245-246 °C. ¹H NMR (CDCl₃; 400 MHz): d 7.38 (m, 1), 7.48 (m, 2), 7.58 (dd, 1, *J* = 1, 6.8), 7.67 (s, 1), 7.72 (dd, 2, *J* = 1.2, 6.4). MS *m/z*: 297.0 (M+1); 295.0 (M-1).



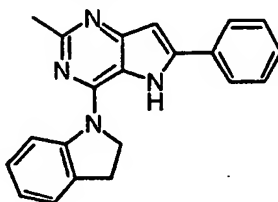
10 **(b) 6-Phenyl-4-piperidyl-2-(trifluoromethyl)thiophene [3,2-d]pyrimidine Hydrochloride.**

To an oven-dried, 50-mL, round-bottomed flask was added methanesulfonylimidazole (prepared by the method described by J. Michalski and co-workers *Phosphorus and Sulfur* 1986, 26, 321.) (67 mg, 0.372 mmol) and THF (10 mL), which was cooled to 0 °C with stirring under N₂. To this solution was added methyl triflate (Aldrich Chemical Company) (42 mL, 0.375 mmol) dropwise. The resulting mixture was stirred at 0 °C for 30 min before a solution of 6-phenyl-2-(trifluoromethyl)thiophene [3,2-d]pyrimidin-4-ol (Example 214(a)) (100 mg, 0.338 mmol) and 1-methylimidazole (22 mL, 0.281 mmol) dissolved in THF (5 mL) was added. The resulting solution was allowed to warm to room temperature over the course of 2 h, and piperidine (0.25 mL, 2.5 mmol) was added dropwise. The mixture was stirred for 30 min and then dissolved in CHCl₃ (50 mL). The organic layer was washed with brine (3 x 50 mL), dried over MgSO₄, filtered, and evaporated to give a residue. The residue was purified by silica gel chromatography with 20% EtOAc/hexanes as eluant to give 80 mg (67% yield)

325

as a light yellow solid. The free base (48 mg, 0.132 mmol) was dissolved in hot CH_2Cl_2 (5 mL) and anhydrous ethereal HCl (0.132 mL, of an 1.0 M soln, 0.132 mmol) was added. The solid was filtered off and dried under vacuum to give 50 mg (95% yield) of a yellow solid.
Mp: 168-169 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 1.7 (br, s, 6), 4.0 (s, 4), 7.52 (m, 3H), 7.91 (d, 2, $J = 7.16$), 8.03 (s, 1). MS m/z : 323.5 (M+1); 321.5 (M-1).

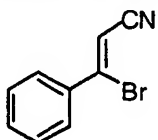
10

Example 215**4-Indolinyl-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine Hydrochloride Hydrate.**

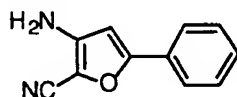
To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (350 mg, 1.44 mmol) and indoline (Aldrich Chemical Company) (350 mg, 2.94 mmol). The flask was purged with N_2 and the mixture was heated to 180 °C for 1 h. The reaction was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with 33% EtOAc/hexanes to give 250 mg (53% yield) of an off white solid. The free base (221 mg, 0.677 mmol) was dissolved in hot EtOAc (15 mL) and MeOH (2 mL) and anhydrous ethereal HCl (0.677 mL, of a 1.0 M soln, 0.677 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 239 mg (97% yield) of the title compound as a light yellow solid. Mp: > 300 °C. ^1H NMR ($\text{DMSO}-d_6$; 400 MHz): δ 2.7 (s, 3), 4.87 (t,

326

- 2, $J = 8.2$), 7.0 (s, 1), 7.17 (t, 1, $J = 7.5$), 7.32 (t, 1, $J = 7.6$), 7.58 (m, 3), 8.0 (d, 2, $J = 6.9$), 8.53 (d, 1, $J = 3.3$), 11.7 (br, 1), 14.55 (br, 1). MS m/z : 327.0 (M+1); 325 (M-1). Anal. Calcd for $C_{21}H_{18}N_4 \cdot 1.0HCl \cdot 1.25H_2O$: C, 65.45; H, 5.62; N, 14.54. Found: C, 65.62; H, 5.62; N, 14.49.

Example 216**10 (a) (2Z)-3-Bromo-3-phenylprop-2-enenitrile.**

- To an oven-dried, 250-mL, round-bottomed flask was added benzyloxyacetonitrile (Avocado Chemical Company) (5.00g, 34.4 mmol) and PBr₃ (100 mL), and the resulting mixture was heated at 170 °C with stirring under N₂.
- 15 After 48 h, the mixture was allowed to cool to room temperature and was carefully poured into ice (500 g) and CHCl₃ (250 mL) was added. The mixture was stirred for 1 h. The layers were separated and the aqueous layer was extracted with CHCl₃ (125 mL). The organic
- 20 layers were combined and washed with saturated NaHCO₃ (3 x 200 mL) and brine (250 mL). The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo to give 8.00 g (98% yield) of a black oil. ¹H NMR (CDCl₃; 400 MHz): d 6.35 (s,1), 7.6 (d, $J = 6.3, 2$), 7.4 (m,3).

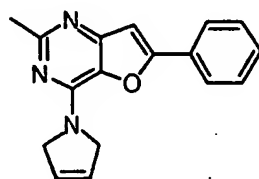


25

(b) 3-Amino-5-phenylfuran-2-carbonitrile.

- To an oven-dried, 150-mL, round-bottomed flask was added glycolonitrile (Aldrich Chemical Company) (4.6 g, 55 wt. % in H₂O, 24.04 mmol), followed by THF (100 mL),
- 30 and MgSO₄ (10 g). The mixture was stirred for 1 h before a soln of (2Z)-3-bromo-3-phenylprop-2-enenitrile

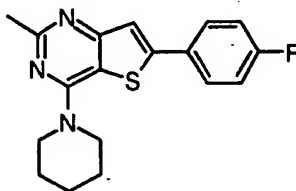
(Example 216(a)) (2.5 g, 12.04 mmol) was added. The mixture was stirred rapidly at room temperature as NaH (1.0 g, 60% in mineral oil, 25 mmol) was carefully added in portions over 1 h. The mixture was poured
5 into ice (100 g) and stirred for 10 min. The reaction was extracted with a mixture of 3:1 of CHCl₃:i-PrOH (3 x 75 mL). The combined organic layers were washed with brine (200 mL), dried over MgSO₄, filtered and evaporated to give 2.0g (90.5% yield) of an oil. ¹H
10 NMR (CDCl₃; 400 MHz): δ 4.01 (br, 2), 6.35 (s, 1), 7.4 (m, 3), 7.63 (d, 2, J = 7.1).



(c) 2-Methyl-6-phenyl-4-(3-pyrrolinyl)furano[3,2-d]pyrimidine Hydrochloride Hydrate.

15 To an oven-dried, 150-mL, round-bottomed flask was added N,N-dimethylacetamide (1.02 mL, 11 mmol) followed by POCl₃ (50 mL). the mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-5-phenylfuran-2-carbonitrile (Example 216 (b))
20 (677 mg, 3.68 mmol). The resulting mixture was heated at 160 °C for 36 h. The solvent was evaporated in vacuo and toluene (50 mL) was added. The solvent was again evaporated in vacuo and to the crude residue was added 3-pyrroline (Aldrich Chemical Company) (2.00 g,
25 28.9 mmol). The reaction was then heated to 120 °C for 1 h and then allowed to cool to room temperature. The crude material was dissolved in CHCl₃ (100 mL) and washed with saturated NaHCO₃ (3 x 100 mL), brine (100 mL), and dried over MgSO₄. The organic layer was
30 filtered, and evaporated in vacuo to give a residue which was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant. The product was isolated

in 550 g (54% yield) as a light yellow solid. The free base (510 mg, 1.84 mmol) was dissolved in hot EtOAc (20 mL) and anhydrous ethereal HCl (1.85 mL, 1.0 M soln, 1.85 mmol) was added dropwise. A precipitate
5 formed immediately and the mixture was allowed to cool to room temperature. The solid was filtered and dried under vacuum to give 565 mg (95% yield) of the title compound. Mp: 279-280 °C. ¹H NMR (DMSO-*d*₆; 500 MHz):
10 δ 2.65 (s, 3), 4.58 (s, 2), 5.01 (s, 2), 6.13 (d, 2, *J* = 20), 7.59 (m, 3), 7.65 (s, 1), 8.13 (d, 2, *J* = 5.9). MS *m/z*: 278.0 (*M*+1). Anal. Calcd for C₁₇H₁₅N₃O•1.10HCl•1.1H₂O: C, 60.54; H, 5.47; N, 12.46; Cl, 11.56. Found: C, 60.58; H, 5.41; N, 12.44; Cl, 11.38.

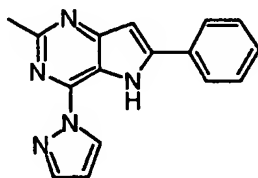


15

Example 217**6-(4-Fluorophenyl)-2-methyl-4-piperidylthiopheno[3,2-d]pyrimidine Hydrochloride Hydrate.**

To an oven-dried, 150-mL, round-bottomed flask was
20 added *N,N*-dimethylacetamide (1.07 mL, 11.5 mmol) followed by POCl₃ (50 mL). The mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-2-cyano-5-(4-fluorophenyl)thiophene (Maybridge Chemical Company) (2.5 g, 11.45 mmol) and the resulting
25 mixture was heated at reflux for 36 h. The reaction was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. The residue was suspended in toluene (50 mL) and again the solvent was evaporated at reduced pressure. Approximately 500 mg of residue was
30 removed and added to an oven-dried, 50-mL, round-bottomed flask, followed by piperidine (10 mL). The flask was purged with N₂, and heated to 160 °C for 2 h.

The flask was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with 33% EtOAc/hexanes to give 250 mg of a light yellow solid. The free base (223 mg, 0.681 mmol) was dissolved in hot EtOAc (10 mL) and anhydrous ethereal HCl (0.68 mL, 1.0 M soln, 0.68 mmol) was added dropwise. A precipitate formed immediately and the reaction was allowed to cool to room temperature and was stirred for an additional 1 h. The light yellow solid was filtered off and dried under vacuum overnight to give 240 mg (97% yield) of a light yellow solid. Mp: 285–287°C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.76 (s,6), 2.63 (s,3), 4.13 (s,4), 7.43 (t,2, *J*=8.8), 7.8 (s,1), 8.01 (m,2). MS *m/z*: 328.0 (*M*+1). Anal. Calcd for C₁₈H₁₈FN₃S•1.25HCl•0.5H₂O: C, 65.48; H, 5.35; N, 10.98; Cl, 11.64. Found: C, 56.48; H, 5.40; N, 10.94; Cl, 11.64.

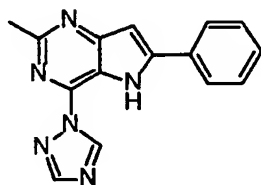


Example 218

20 2-Methyl-6-phenyl-4-pyrazolopyrrolo[3,2-*d*]pyrimidine Hydrochloride Hydrate.

To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine (Example 1(e)) (350 mg, 1.44 mmol) followed by pyrazole (Aldrich Chemical Company) (196 mg, 2.88 mmol) and solid Na₂CO₃ (610 mg, 5.76 mmol). The flask was purged with N₂ and heated to 190–200 °C for 4 h. The reaction was allowed to cool to room temperature and the residue was dissolved in MeOH (25 mL). The remaining salts were filtered off and the organic layer evaporated under reduced pressure. The residue was purified by silica gel chromatography with EtOAc as

eluant to give 245 mg (62% yield) of an off white solid. The free base (238 mg, 0.865 mmol) was dissolved in hot EtOAc (15 mL) and anhydrous ethereal HCl (0.87 mL, 1.0 M soln, 0.87 mmol) was added dropwise. A precipitate formed and the reaction was allowed to cool to room temperature and stirred for 1 h. The solid was filtered off and dried under vacuum at 60 °C overnight to give 250 mg (93% yield) of an off white solid. Mp: 253-254°C. ¹H NMR (DMSO-d₆; 400 MHz): δ 2.8 (s, 3), 6.83 (s, 1), 7.23 (s, 1), 7.58 (m, 3), 8.12 (d, 2, J = 6.4), 8.22 (s, 1), 8.88 (d, 1, J = 2.5), 12.0 (br s, 1). MS m/z: 276.0 (M+1). Anal. Calcd for C₁₆H₁₃N₅•1.11HCl•0.9H₂O: C, 57.86; H, 4.83; N, 21.09; Cl, 11.88. Found: C, 58.01; H, 4.88; N, 20.79; Cl, 11.88.



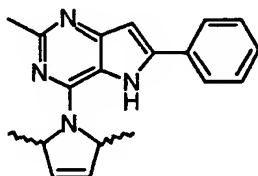
Example 219

2-Methyl-6-phenyl-4-[1,2,4-triazolyl]pyrrolo[3,2-d]pyrimidine Hydrochloride.

To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (350 mg, 1.44 mmol) followed by 1,2,4-triazole (Aldrich Chemical Company) (200 mg, 2.88 mmol) and solid Na₂CO₃ (610 mg, 5.76 mmol). The flask was purged with N₂ and heated to 190-200 °C for 4 h. The reaction was allowed to cool to room temperature and the residue was dissolved in MeOH (25 mL). The remaining salts were filter off and the organic layer evaporated under reduced pressure. The residue was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant to give 180 mg (45% yield) of an off white solid. The free base (168 mg, 0.608

331

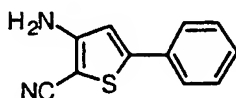
mmol) was dissolved in hot EtOAc (15 mL) and anhydrous
ethereal HCl (0.61 mL, 1.0 M soln, 0.61 mmol) was
added dropwise. A precipitate formed and the reaction
was allowed to cool to room temperature and stirred for
5 1 h. The solid was filtered off and dried under vacuum
at 60 °C overnight to give 182 mg (96% yield) of an off
white solid. Mp: 264-265 °C. ¹H NMR (DMSO-*d*₆; 400
MHz): d 2.77 (s, 3), 7.22 (s, 1), 7.57 (m, 3), 8.10
(d, 2, *J* = 5.5), 8.6 (d, 1, *J* = 3.4), 9.64 (d, 1, *J* =
10 4.2), 11.87 (br m, 1). MS *m/z*: 277.0 (*M*+1); 275 (*M*-1).

**Example 220****4-(2,5-Dimethyl(3-pyrrolinyl))-2-methyl-6-phenylpyrrolo
15 [3,2-*d*]pyrimidine Hydrochloride Hydrate.**

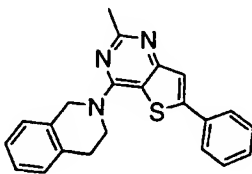
To an oven-dried, 50-mL, round-bottomed flask was
added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-*d*]
pyrimidine (Example 1(e)) (600 mg, 2.46 mmol) and a *cis*
and *trans* mixture of 2,5-dimethyl-3-pyrroline (Aldrich
20 Chemical Company) (717 mg, 7.38 mmol). The flask was
purged with N₂ and the mixture was heated to 180 °C for
1 h. The reaction was allowed to cool to room
temperature and the crude material triturated with MeOH
to give 550 mg (73% yield) of an off white solid. The
25 free base (500 mg, 1.64 mmol) was dissolved in hot
EtOAc (15 mL) and MeOH (2 mL) and anhydrous ethereal HCl
(1.64 mL, of a 1.0 M soln, 1.64 mmol) was added
dropwise. The mixture was stirred for 2 h and allowed
to cool to room temperature. The resulting solid was
30 filtered and dried under high vacuum to give 550 mg
(98% yield) of the title compound as a light yellow
solid. Mp: 242-243 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): d

332

1.42 (d, 6, $J = 6.3$), 2.54 (s, 3), 5.14 (br, 1), 5.65 (br, 1), 6.00 (s, 2), 6.84 (s, 1), 7.5 (m, 3), 7.85 (d, 2, $J = 7.0$). MS m/z : 358 (M+1). Anal. Calcd for $C_{15}H_{20}N_4 \cdot 1.0 \text{ HCl} \cdot 0.90 \text{ H}_2\text{O}$: C, 63.91; H, 6.44; N, 15.69; Cl, 9.93. Found: C, 64.01; H, 6.20; N, 15.5; Cl, 9.78.

Example 221**(a) 3-Amino-5-phenylthiophene-2-carbonitrile.**

To an oven-dried, 50-mL, round-bottomed flask was added acetylmercaptoacetonitrile (Maybridge Chemical Company) (2.00 g, 17.37 mmol), followed by anhydrous EtOH (50 mL) and the dropwise addition of NaOCH₃ (5.64 g, 21 wt. %, 17.37 mmol). The resulting mixture was stirred for 1 h at room temperature, and then cooled to -78 °C with a dry ice/acetone bath. To this solution was added an ethanolic solution of vinyl bromide example 33 a (3.8 g, 18.26 mmol) in anhydrous EtOH (10 mL) at -78 °C. After stirring for 1 h at this temperature, the reaction was allowed to warm to room temperature and was stirred for an additional 2 h. The solvent was evaporated under reduced pressure to leave a residue. The residue was dissolved in CHCl₃ (100 mL) and washed with 2.0 N NaOH (3 x 75 mL), and brine (100 mL). The organic layer was dried over MgSO₄, filtered, and evaporated to give a brown solid in 3.4 g (98% yield). ¹H NMR (DMSO-*d*₆; 400 MHz): d 4.48 (br, 2), 6.75 (s, 1), 7.39 (m, 3), 7.53 (dd, 2, $J = 2, 6$). MS m/z : 201 (M+1).

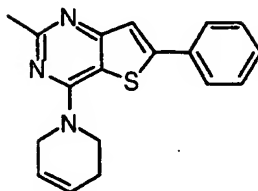


30

**(b) 2-Methyl-6-phenyl-4-[2-1,2,3,4-tetrahydro
isoquinolyl]thiopheno[3,2-d]pyrimidine Hydrochloride
Hydrate.**

To an oven-dried, 150-mL, round-bottomed flask was
5 added *N,N*-dimethylacetamide (Aldrich Chemical Company)
(1.07 mL, 11.5 mmol) followed by POCl₃ (50 mL). The
mixture was stirred at room temperature for 1 h. To
this mixture was added 3-amino-2-cyano-5-phenyl
thiophene (Example 221(a)) (2.5 g, 11.45 mmol) and the
10 resulting mixture was heated at reflux for 36 h. The
reaction was allowed to cool to room temperature and
the solvent was evaporated *in vacuo*. The residue was
suspended in toluene (50 mL) and again the solvent was
evaporated at reduced pressure. Approximately 750 mg
15 of residue was removed and added to an oven-dried, 50-
mL, round-bottomed flask, followed by 1,2,3,4-
tetrahydroisoquinoline (4.0 mL, 31.9 mmol). The flask
was purged with N₂, and heated to 160 °C for 2 h. The
flask was allowed to cool to room temperature and the
20 crude material was purified by silica gel
chromatography with 25% EtOAc/hexanes to give 250 mg
of a light yellow solid. The free base (500 mg, 1.4
mmol) was dissolved in hot EtOAc (20 mL) and anhydrous
ethereal HCl (1.4 mL, 1.0 M soln, 1.4 mmol) was added
25 dropwise. A precipitate formed immediately and the
reaction was allowed to cool to room temperature and
was stirred for an additional 1 h. The light yellow
solid was filtered off and dried under vacuum overnight
to give 540 mg (98% yield) of a light orange solid.
30 Mp: 263–265 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 2.55 (s,
3), 3.00 (s, 2), 4.19 (t, 2, *J* = 5.7), 5.15 (s, 2),
7.17 (m, 3), 7.28 (d, 1, *J* = 4.0), 7.45 (m, 3), 7.71
(s, 1), 7.80 (m, 2). MS *m/z*: 375.0 (M+1). Anal. Calcd
for C₂₂H₁₉N₃S•1.0HCl•0.88H₂O: C, 64.38; H, 5.35; N, 10.24;
35 Cl, 8.77. Found: C, 64.38; H, 5.10; N, 10.14; Cl, 8.76.

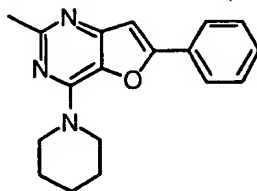
Example 222

**2-Methyl-6-phenyl-4-(1,2,5,6-tetrahydropyridyl)****5 thiopheno[3,2-d]pyrimidine Hydrochloride Hydrate.**

To an oven-dried, 150-mL, round-bottomed flask was added *N,N*-dimethylacetamide (Aldrich Chemical Company) (1.07 mL, 11.5 mmol) followed by POCl₃ (50 mL). The mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-2-cyano-5-phenyl thiophene (Example 221(a)) (2.5 g, 11.45 mmol) and the resulting mixture was heated at reflux for 36 h. The reaction was allowed to cool to room temperature and the solvent was evaporated *in vacuo*. The residue was suspended in toluene (50 mL) and again the solvent was evaporated at reduced pressure. Approximately 750 mg of residue was removed and added to an oven-dried, 50-mL, round-bottomed flask, followed by 1,2,3,6-tetrahydropyridine (3.0 mL, 32.9 mmol). The flask was purged with N₂, and heated to 160 °C for 2 h. The flask was allowed to cool to room temperature and the crude material was purified by silica gel chromatography with 25% EtOAc/hexanes to give 325 mg of a light yellow solid. The free base (300 mg, 0.976 mmol) was dissolved in hot EtOAc (15 mL) and anhydrous ethereal HCl (1.0 mL, 1.0 M soln, 1.0 mmol) was added dropwise. A precipitate formed immediately and the reaction was allowed to cool to room temperature and was stirred for an additional 1 h. The light yellow solid was filtered off and dried under vacuum overnight to give 320 mg (95.5% yield) of a light yellow solid. Mp: 279–281 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): d 2.59 (br s, 2), 2.85 (s,

335

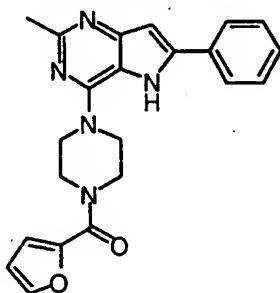
3), 4.42 (t, 2, $J = 5.7$), 4.87 (s, 2), 6.09 (d, 1, $J = 10$), 6.23 (d, 1, $J = 9.9$), 7.78 (m, 3), 8.04 (s, 1), 8.15 (m, 2). MS m/z : 308.0 ($M+1$). Anal. Calcd for $C_{18}H_{17}N_3S \cdot 1.0HCl \cdot 0.65H_2O$: C, 60.73; H, 5.47; N, 11.81; Cl, 10.05. Found: C, 60.73; H, 5.32; N, 11.61; Cl, 9.95.

**Example 223****2-Methyl-6-phenyl-4-piperidylfurano[3,2-d]pyrimidine Hydrochloride Hydrate.**

To an oven-dried, 150-mL, round-bottomed flask was added *N,N*-dimethylacetamide (1.02 mL, 11 mmol) followed by POCl₃ (50 mL). The mixture was stirred at room temperature for 1 h. To this mixture was added 3-amino-5-phenylfuran-2-carbonitrile (Example 216(b)) (677 mg, 3.68 mmol). The resulting mixture was heated at 160 °C for 36 h. The solvent was evaporated in vacuo and toluene (50 mL) was added. The solvent was again evaporated in vacuo and to the crude residue was added piperidine (Aldrich Chemical Company) (3.00 mL, 30.3 mmol). The reaction was then heated to 160 °C for 1 h and then allowed to cool to room temperature. The crude material was dissolved in CHCl₃ (100 mL) and washed with saturated NaHCO₃ (3 x 100 mL), brine (100 mL), and dried over MgSO₄. The organic layer was filtered, and evaporated in vacuo to give a residue which was purified by silica gel chromatography with 50% EtOAc/hexanes as eluant. The product was isolated in 200 mg (19% yield) as a light yellow solid. The free base (181 mg, 0.617 mmol) was dissolved in hot EtOAc (20 mL) and anhydrous ethereal HCl (0.617 mL, 1.0 M soln, 0.617 mmol) was added dropwise. A precipitate

formed immediately and the mixture was allowed to cool to room temperature. The solid was filtered and dried under vacuum to give 198 mg (97% yield) of the title compound. Mp: > 290 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.75 (br s, 6), 2.58 (s, 3), 4.16 (s, 4), 7.61 (m, 4), 8.08 (d, 2, J = 6.8). MS m/z: 294.0 (M+1). Anal. Calcd for C₁₆H₁₉N₃O•1.08 HCl•1.82 H₂O. C, 59.11; H, 6.54; N, 11.49; Cl, 10.51. Found: C, 59.11; H, 6.19; N, 11.42; Cl, 10.62.

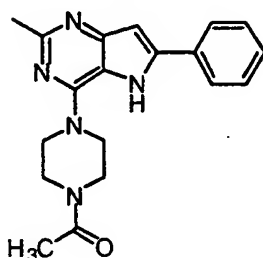
10

Example 224**1-(2-Furanylcarbonyl)-4-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)piperazine Hydrochloride Monohydrate.**

15 To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (500 mg, 2.05 mmol) and the 1-(2-furoyl)piperazine (Avocado Chemical Company) (810 mg, 4.10 mmol). The flask was purged with N₂ and the mixture was heated to 180 °C for 30 min. The reaction was allowed to cool to room temperature and the crude material was purified by flash chromatography on silica gel with 50% EtOAc/CHCl₃ as eluant to give 500 mg (63% yield) of an off white solid. The free base (200 mg, 25 0.52 mmol) was dissolved in hot EtOAc (10 mL) and anhydrous ethereal HCl (0.52 mL, of a 1.0 M soln, 0.52 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high

vacuum to give 205 mg (96% yield) of the title compound as a light yellow solid. Mp: 192-193 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 2.54 (s, 3), 3.89 (br s, 4), 4.17 (t, 4, J = 4.3), 6.62 (q, 1, J = 1.7), 6.9 (s, 1), 7.05 (d, 1, J = 3.4), 7.4 (m, 3), 7.85 (s, 1), 7.93 (d, 2, J = 6.92). MS m/z: 388 (M+1). Anal. Calcd for C₂₂H₂₁N₅O₂•HCl•H₂O: C, 59.79; H, 5.47; N, 15.85; O, 10.86; Cl, 8.02. Found: C, 59.99; H, 5.33; N, 15.79; Cl, 8.06.

10

Example 225**1-Acetyl-4-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)piperazine Hydrochloride.**

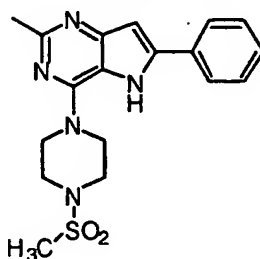
15 To an oven-dried, 50-mL, round-bottomed flask was added 4-chloro-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine (Example 1(e)) (500 mg, 2.05 mmol) and 1-acetyl-piperazine (Aldrich Chemical Company) (525 mg, 4.10 mmol). The flask was purged with N₂ and the mixture was heated to 180 °C for 30 min. The reaction was allowed to cool to room temperature and the crude material was purified by flash chromatography on silica gel with 10% MeOH/EtOAc as eluant to give 600 mg (87% yield) of an off-white solid. The free base (400 mg, 1.2 mmol) was dissolved in hot EtOAc (10 mL) and anhydrous ethereal HCl (1.2 mL, of a 1.0 M soln, 1.2 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 205 mg (96% yield) of the title compound

20

25

30

as a light yellow solid. Mp: 282-283 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 2.09 (s, 3), 2.61 (s, 3), 3.7 (s, 4), 4.14 (dt, *J* = 5.3, 14), 6.95 (s, 1), 7.54 (m, 3), 8.00 (d, 2, *J* = 6.88). MS *m/z*: 366 (M+1); 364 (M-1). Anal. Calcd for C₁₉H₂₁N₅O•HCl.: C, 60.76; H, 5.95; N, 18.65; O, 4.45; Cl, 10.19. Found: C, 60.76; H, 5.90; N, 18.64; Cl, 10.15.

Example 226

10

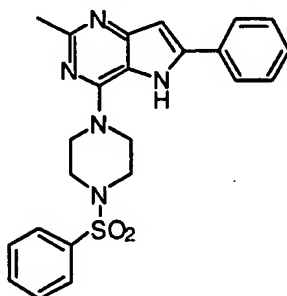
1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-4-(methylsulfonyl)piperazine Hydrochloride Monohydrate.

To an oven-dried, 50-mL, round-bottomed flask was added 2-methyl-6-phenyl-4-piperazinylpyrrolo[3,2-d]pyrimidine (Example 26) (400 mg, 1.36 mmol) was suspended in anhydrous THF (20 mL) and Et₃N (0.4 mL, 2.8 mmol) was added. The mixture was cooled to 0 °C and methanesulfonyl chloride (Aldrich Chemical Company) (0.12 mL, 1.5 mmol) was added dropwise and allowed to warm to room temperature over 30 min. EtOAc (50 mL) was added to the mixture which was extracted with saturated NaHCO₃ (3 x 50 mL). The organic layer was washed with saturated NaCl (75 mL), dried over MgSO₄, filtered and evaporated in vacuo to give 450 mg (89% yield) as a light yellow solid. The free base (440 mg, 1.2 mmol) was dissolved in hot EtOAc (20 mL) and anhydrous ethereal HCl (1.18 mL, of a 1.0 M soln, 1.18 mmol) was added dropwise. The mixture was stirred for 2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high

30

vacuum to give 460 mg (95.6% yield) of the title compound as a light yellow solid. Mp: 280-282 °C. ¹H NMR (DMSO-d₆; 400 MHz); δ 2.54 (s, 3), 2.88 (s, 3), 3.29 (s, 4), 4.13 (t, 4, J = 4.62), 6.9 (s, 1), 7.51 (m, 3), 7.94 (d, 2, J = 6.85). MS m/z: 372 (M+1); 370 (M-1). Anal. Calcd for C₁₈H₂₁N₅O₂S•HCl•H₂O.: C, 50.46; H, 5.70; N, 16.35; Cl, 8.41. Found: C, 50.71; H, 5.60; N, 16.22; Cl, 8.45.

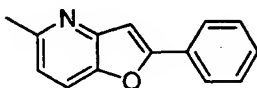
10

Example 227**1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(phenylsulfonyl)piperazine Hydrochloride Monohydrate.**

To an oven-dried, 50-mL, round-bottomed flask was added 2-methyl-6-phenyl-4-piperazinylpyrrolo[3,2-d]pyrimidine (Example 26) (400 mg, 1.36 mmol) was suspended in anhydrous THF (20 mL) and Et₃N (0.4 mL, 2.8 mmol) was added. The mixture was cooled to 0 °C and benzenesulfonyl chloride (Aldrich Chemical Company) (0.19 mL, 1.5 mmol) was added dropwise and allowed to warm to room temperature over 30 min. EtOAc (50 mL) was added to the mixture which was extracted with saturated NaHCO₃ (3 x 50 mL). The organic layer was washed with saturated NaCl (75 mL), dried over MgSO₄, filtered and evaporated in vacuo to give 450 mg (89% yield) as a light yellow solid. The free base (500 mg, 1.15 mmol) was dissolved in hot EtOAc (20 mL) and anhydrous ethereal HCl (1.15 mL, of a 1.0 M soln, 1.15 mmol) was added dropwise. The mixture was stirred for

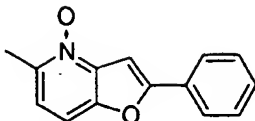
340

2 h and allowed to cool to room temperature. The resulting solid was filtered and dried under high vacuum to give 510 mg (94.1% yield) of the title compound as a light yellow solid. Mp: 242-243 °C. ¹H NMR (DMSO-d₆; 400 MHz); δ 2.4 (s, 3), 2.98 (t, 4, J = 4.6), 4.00 (t, 4, J = 4.7), 6.75 (s, 1), 7.37 (m, 3), 7.49 (t, 2, J = 7.8), 7.57 (t, 1, J = 7.5), 7.62 (d, 2, J = 7.2), 7.81 (d, 2, J = 6.7). MS m/z: 434 (M+1); 432 (M-1). Anal. Calcd for C₂₃H₂₄N₅O₂S•HCl•H₂O: C, 56.63; H, 5.37; N, 14.36; Cl, 7.27. Found: C, 56.63; H, 5.37; N, 14.27; Cl, 7.41.

Example 228**(a) 5-Methyl-2-phenylfurano[3,2-b]pyridine.**

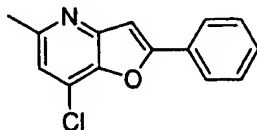
A mixture of 6-iodo-2-picolin-5-ol (Aldrich Chemical Company) (1.00 g, 4.29 mmol), phenylacetylene (Aldrich Chemical Company) (0.66 mL, 6.01 mmol), Cl₂Pd(PPh₃)₂ (15.1 mg, 0.21 mmol) and CuI (41.0 mg, 0.21 mmol) in Et₃N (20 mL) was heated under reflux (100 °C) for 16 h. Heating was discontinued and after cooling the mixture was diluted with CH₂Cl₂ (100 mL) and NH₄Cl (50 mL). The mixture was transferred to a separatory funnel. The organic solution was collected, washed with saturated NH₄Cl (50 mL) and saturated NaCl (50 mL). The organic solution was collected, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 821 mg (91%) of the title compound as a white colored solid. ¹H NMR (CDCl₃; 400 MHz): δ 2.63 (s, 3), 7.07 (d, 1, J = 8.4), 7.15 (s, 1), 7.40 (dt, 1, J = 2.1, 7.4), 7.47 (t, 2, J = 7.8), 7.67 (d,

1, $J = 8.6$), 7.90 (dd, 2, $J = 1.5$, 7.2). MS m/z : 210 (M+1).



(b) 5-Methyl-2-phenylfurano[3,2-b]pyridine N-oxide.

5 A mixture of 5-methyl-2-phenylfurano[3,2-b]pyridine (Example 228(a)) (507 mg, 2.43 mmol) and *m*-chloroperbenzoic acid (0.84 g, purity 60%, 2.91 mmol) in CHCl_3 (20 mL) was stirred at 25 °C for 18 h. The mixture was filtered slowly through a fritted funnel
10 with a basic alumina (20 g) pad. The pad was washed with CHCl_3 (50 mL) and the organic solutions were combined and concentrated under reduced pressure to afford 517 mg (95%) of the title compound as a white colored solid. ^1H NMR (CDCl_3 ; 400 MHz): δ 2.64 (s, 3),
15 7.15 (d, 1, $J = 8.4$), 7.40 (d, 1, $J = 8.4$), 7.43 - 7.51 (m, 4), 7.89 (dd, 2, $J = 1.4$, 7.0). MS m/z : 226 (M+1).

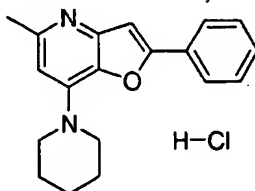


(c) 7-Chloro-5-methyl-2-phenylfurano[3,2-b]pyridine.

20 To a mixture of 5-methyl-2-phenylfurano[3,2-b]pyridine *N*-oxide (Example 228(b)) (302 mg, 1.33 mmol) in CHCl_3 (4 mL) was added POCl_3 (1.3 mL, 13.3 mmol). The mixture was heated to 60 °C where it was stirred for 16 h. After cooling the reaction mixture was
25 poured onto crushed ice (50 mL). The pH of the mixture was adjusted to pH 8 with the slow addition of saturated NaHCO_3 (15 mL). CHCl_3 (30 mL) was added and the mixture was transferred to a separatory funnel. The organic solution was collected and the aqueous
30 solution washed with CHCl_3 (2 x 30 mL). The organic solutions were combined, dried over MgSO_4 , filtered and

342

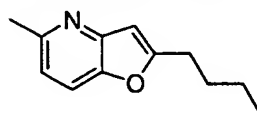
concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 25:75 EtOAc:hexanes as elutant to give 220 mg (68%) of the title compound as a white solid. ¹H NMR (CDCl₃; 400 MHz): δ 2.63 (s, 3), 7.10 (s, 1), 7.15 (s, 1), 7.43 (t, 1, J = 7.3), 7.49 (t, 2, J = 7.8), 7.93 (d, 2, J = 7.9). MS m/z : 244 (M+1).



(d) 5-Methyl-2-phenyl-7-piperidylfurano[3,2-b]pyridine hydrochloride.

To a mixture of 7-chloro-5-methyl-2-phenylfurano [3,2-b]pyridine (Example 228(c)) (365 mg, 1.50 mmol) and piperidine (5 mL, 50.5 mmol) was added DMF (2 mL). Mixture stirred at 120 °C under N₂ for 26 h. After cooling, the reaction mixture was concentrated. The residue was diluted with H₂O (70 mL) and Et₂O (50 mL). The mixture was transferred to a separatory funnel and the organic solution was collected. The aqueous solution was washed with Et₂O (2 x 40 mL). The organic solutions were combined, washed with H₂O (50 mL), saturated NaCl (70 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 300 mg (68%) of 5-methyl-2-phenyl-7-piperidylfurano[3,2-b]pyridine as a cream colored solid. This material (298 mg, 1.02 mmol) was dissolved in EtOAc (20 mL) and heated to boiling. To the hot solution was added 1M ethereal HCl (1.00 mL, 1.00 mmol). The solution was left to cool to 25 °C. The resulting solid was collected by filtration, washed with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 25 °C to give 290 mg (59%) of the title

compound as a white colored powder. Mp: >280 °C. ¹H NMR (DMSO-*d*₆; 400 MHz): δ 1.67 (br s, 6), 2.49 (s, 3), 3.94 (br s, 4), 6.93 (s, 1), 7.46 - 7.54 (m, 4), 7.98 (dd, 2, *J* = 1.5, 7.6), 14.14 (s, 1). MS *m/z* : 293 (*M*+1 for free base). Anal. Calcd for C₁₉H₂₀N₂O•HCl•0.25H₂O: C, 68.46; H, 6.50; N, 8.41; Cl, 10.64. Found C, 68.60; H, 6.44; N, 8.43; Cl, 10.56.

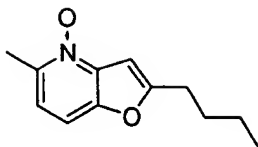
Example 229

10

(a) 2-Butyl-5-methylfurano[3,2-b]pyridine.

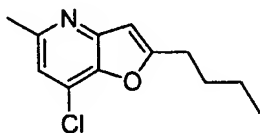
A mixture of 6-iodo-2-picolin-5-ol (Aldrich Chemical Company) (1.49 g, 6.33 mmol), 1-hexyne (Aldrich Chemical Company) (1.02 mL, 8.86 mmol), Cl₂Pd(PPh₃)₂ (220 mg, 0.32 mmol) and CuI (60.0 mg, 0.32 mmol) in Et₃N (25 mL) was heated under reflux (90 °C) for 18 h. Heating was discontinued and after cooling the mixture was diluted with CH₂Cl₂ (100 mL) and NH₄Cl (50 mL). The mixture was transferred to a separatory funnel. The organic solution was collected, washed with saturated NH₄Cl (50 mL) and saturated NaCl (50 mL). The organic solution was collected, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 1.08 g (92%) of the title compound as a yellow colored oil. ¹H NMR (CDCl₃; 400 MHz): δ 0.94 (t, 3, *J* = 7.4), 1.43 (hextet, 2, *J* = 7.5), 1.74 (quintet, 2, *J* = 7.6), 2.62 (s, 3), 2.79 (t, 2, *J* = 7.6), 6.52 (s, 1), 6.99 (d, 1, *J* = 8.4), 7.53 (d, 1, *J* = 8.4). MS *m/z* : 190 (*M*+1).

344



(b) 2-Butyl-5-methylfurano[3,2-b]pyridine N-oxide.

A mixture of 2-butyl-5-methylfurano[3,2-b]pyridine (Example 229(a)) (1.06 g, 5.61 mmol) and *m*-chloroperbenzoic acid (1.94 g, purity 60%, 6.73 mmol) in CHCl₃ (50 mL) was stirred at 25 °C for 18 h. The mixture was filtered slowly through a fritted funnel with a basic alumina (30 g) pad. The pad was washed with CHCl₃ (50 mL) and the organic solutions were combined and concentrated under reduced pressure to afford 1.14 g (99%) of the title compound as a yellow colored oil. ¹H NMR (CDCl₃; 400 MHz): δ 0.95 (t, 3, *J* = 7.3), 1.41 (hextet, 2, *J* = 7.4), 1.74 (quintet, 2, *J* = 7.5), 2.60 (s, 3), 2.81 (t, 2, *J* = 7.5), 6.86 (s, 1), 7.07 (d, 1, *J* = 8.4), 7.26 (d, 1, *J* = 8.4). MS *m/z* : 207 (*M*+1).

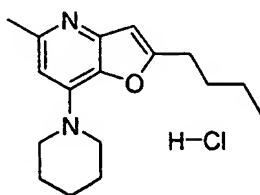


(c) 2-Butyl-7-chloro-5-methylfurano[3,2-b]pyridine.

To a mixture of 2-butyl-5-methylfurano[3,2-b]pyridine *N*-oxide (Example 229(b)) (1.13 g, 5.51 mmol) in CHCl₃ (3 mL) was added POCl₃ (5.1 mL, 55.1 mmol). The mixture was heated to 80 °C where it was stirred for 16 h. After cooling the reaction mixture was poured onto crushed ice (100 mL). The pH of the mixture was adjusted to pH 8 with the slow addition of saturated NaHCO₃ (150 mL). CHCl₃ (150 mL) was added and the mixture was transferred to a separatory funnel. The organic solution was collected and the aqueous solution washed with CHCl₃ (2 x 70 mL). The organic solutions were combined, dried over MgSO₄, filtered and

concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 10:90 EtOAc:hexanes as elutant to give 671 mg (54%) of the title compound as a white colored solid. ¹H NMR

- 5 (CDCl₃; 400 MHz): δ 0.96 (t, 3, J = 7.4), 1.43 (hextet, 2, J = 7.4), 1.76 (quintet, 2, J = 7.5), 2.60 (s, 3), 2.83 (t, 2, J = 7.7), 6.54 (s, 1), 7.02 (s, 1). MS m/z : 224 (M+1).



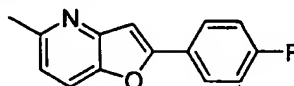
10 **(d) 2-Butyl-5-methyl-7-piperidylfurano[3,2-b]pyridine hydrochloride.**

- To a mixture of 2-butyl-7-chloro-5-methylfurano [3,2-b]pyridine (Example 229(c)) (329 mg, 1.45 mmol) and piperidine (3 mL, 30.4 mmol) was added a mixture of
- 15 K₂CO₃ (0.85 g, 5.8 mmol) in H₂O (1 mL). Mixture stirred at 100 °C under N₂ for 16 h. After cooling, the reaction mixture was concentrated. The residue was diluted with H₂O (70 mL) and Et₂O (50 mL). The mixture was transferred to a separatory funnel and the organic
- 20 solution was collected. The aqueous solution was washed with Et₂O (2 x 40 mL). The organic solutions were combined, washed with H₂O (50 mL), saturated NaCl (70 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by
- 25 flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 310 mg (77%) of 2-butyl-5-methyl-7-piperidylfurano[3,2-b]pyridine as a cream colored solid. This material (310 mg, 1.12 mmol) was dissolved in EtOAc (10 mL) and heated to boiling.
- 30 To the hot solution was added 1M ethereal HCl (1.20 mL, 1.20 mmol). The solution was left to cool to 25 °C. The resulting solid was collected by filtration, washed

346

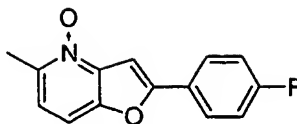
with EtOAc (2 x 5 mL), Et₂O (3 x 5 mL) and dried under vacuum at 25 °C to give 311 mg (69%) of the title compound as a white colored powder. Mp: 172 - 173 °C.

¹H NMR (CDCl₃; 400 MHz): δ 0.95 (t, 3, J = 7.4), 1.42 (hextet, 2, J = 7.3), 1.69 (quintet, 2, J = 7.7), 1.79 (br s, 6), 2.71 (s, 3), 2.79 (t, 2, J = 7.5), 3.85 (br , 4), 6.29 (s, 1), 7.01 (s, 1), 15.56 (s, 1). MS m/z : 2793 (M+1 for free base). Anal. Calcd for C₁₇H₂₄N₂O•HCl•0.5H₂O: C, 64.24; H, 8.25; N, 8.82; Cl, 11.15. Found C, 64.42; H, 8.23; N, 8.75; Cl, 11.26.

Example 230 and Example 231**(a) 2-(4-Fluorophenyl)-5-methylfurano[3,2-b]pyridine.**

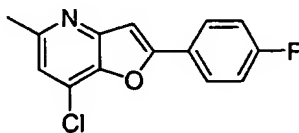
A mixture of 6-iodo-2-picolin-5-ol (Aldrich Chemical Company) (1.38 g, 5.86 mmol), 1-ethynyl-4-fluorobenzene (Aldrich Chemical Company) (0.99 g, 8.21 mmol), Cl₂Pd(PPh₃)₂ (205 mg, 0.29 mmol) and CuI (56 mg, 0.29 mmol) in Et₃N (25 mL) was heated under reflux (90 °C) for 16 h. Heating was discontinued and after cooling the mixture was diluted with CH₂Cl₂ (100 mL) and NH₄Cl (50 mL). The mixture was transferred to a separatory funnel. The organic solution was collected, washed with saturated NH₄Cl (50 mL) and saturated NaCl (50 mL). The organic solution was collected, dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 1.17 g (88%) of the title compound as a white colored solid. ¹H NMR (CDCl₃; 400 MHz): δ 2.66 (s, 3), 7.08 (s, 1), 7.17 (t, 2, J = 6.7), 7.66 (d, 1, J = 8.3), 7.84 - 7.89 (m, 2). MS m/z : 228 (M+1).

347



(b) 2-(4-Fluorophenyl)-5-methylfurano[3,2-b]pyridine N-oxide.

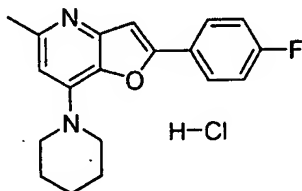
A mixture of 2-(4-fluorophenyl)-5-methylfurano
5 [3,2-b]pyridine (Example 230(a)) (1.15 g, 5.07 mmol)
and *m*-chloroperbenzoic acid (1.75 g, purity 60%, 6.08
mmol) in CHCl₃ (40 mL) was stirred at 25 °C for 18 h.
The mixture was filtered slowly through a fritted
funnel with a basic alumina (40 g) pad. The pad was
10 washed with CHCl₃ (2 x 50 mL) and the organic solutions
were combined and concentrated under reduced pressure
to afford 1.23 mg (95%) of the title compound as a
white solid. ¹H NMR (CDCl₃; 400 MHz): δ 2.63 (s, 3),
7.13 - 7.21 (m, 3), 7.39 (d, 1, *J* = 8.4), 7.41 (s, 1),
15 7.85 - 7.89 (m, 2). MS *m/z* : 244 (M+1).



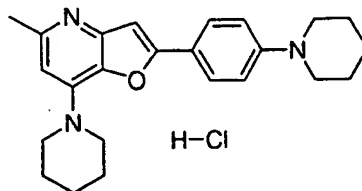
(c) 7-Chloro-2-(4-fluorophenyl)-5-methylfurano[3,2-b]pyridine.

To a mixture of 2-(4-fluorophenyl)-5-methylfurano
20 [3,2-b]pyridine *N*-oxide (Example 230(b)) (1.22 g, 5.02
mmol) in CHCl₃ (2 mL) was added POCl₃ (5.0 mL, 50.2
mmol). The mixture was heated to 100 °C where it was
stirred for 8 h. After cooling the reaction mixture
was poured onto crushed ice (50 mL). The pH of the
25 mixture was adjusted to pH 8 with the slow addition of
saturated NaHCO₃ (100 mL). CHCl₃ (100 mL) was added and
the mixture was transferred to a separatory funnel.
The organic solution was collected and the aqueous
solution washed with CHCl₃ (2 x 70 mL). The organic
30 solutions were combined, dried over MgSO₄, filtered and
concentrated under reduced pressure. The residue was

purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 775 mg (59%) of the title compound as a white colored solid. ¹H NMR (CDCl₃; 400 MHz): δ 2.63 (s, 3), 7.09 (s, 1), 7.11 (s, 1), 7.18 (t, 2, J = 8.6), 7.89 - 7.93 (m, 2). MS m/z : 262 (M+1).



Example 230



Example 231

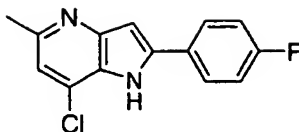
(d) 2-(4-Fluorophenyl)-5-methyl-7-piperidylfurano[3,2-b]pyridine hydrochloride (Example 230) and 5-Methyl-7-piperidyl-2-(4-piperidylphenyl)furano[3,2-b]pyridine hydrochloride (Example 231).

To a mixture of 7-chloro-5-methyl-2-phenylfurano[3,2-b]pyridine (Example 230(c)) (370 mg, 1.43 mmol) and piperidine (5 mL, 50.5 mmol) was added DMF (2 mL). Mixture stirred at 120 °C under N₂ for 24 h. After cooling, the reaction mixture was concentrated. The residue was diluted with H₂O (70 mL) and Et₂O (50 mL). The mixture was transferred to a separatory funnel and the organic solution was collected. The aqueous solution was washed with Et₂O (2 x 40 mL). The organic solutions were combined, washed with H₂O (50 mL), saturated NaCl (70 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel with 50:50 EtOAc:hexanes as elutant to give 132 mg (30%) of 2-(4-fluorophenyl)-5-methyl-7-piperidylfurano[3,2-b]pyridine as a cream colored solid and 35 mg (7%) of 5-methyl-7-piperidyl-2-(4-piperidylphenyl)furano[3,2-b]pyridine as a tan colored solid.

Example 230: 2-(4-Fluorophenyl)-5-methyl-7-piperidylfurano[3,2-b]pyridine (132 mg, 0.42 mmol) was dissolved in EtOAc (5 mL) and heated to boiling. To the hot solution was added 1M ethereal HCl (0.50 mL, 0.5 mmol). The solution was left to cool to 25 °C. The resulting solid was collected by filtration, washed with EtOAc (2 x 2 mL), Et₂O (3 x 5 mL) and dried under vacuum at 25 °C to give 130 mg (27%) of the title compound as a cream colored powder. Mp: >280 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.68 (br s, 6), 2.48 (s, 3), 3.94 (br s, 4), 6.95 (s, 1), 7.39 (t, 2, J = 8.6), 7.50 (s, 1), 8.07 (m, 2), 13.85 (s, 1). MS m/z : 311 (M+1 for free base). Anal. Calcd for C₁₉H₁₉FN₂O•HCl•0.25H₂O: C, 64.95; H, 5.88; N, 7.98; Cl, 10.09. Found C, 65.18; H, 5.86; N, 7.93; Cl, 10.13.

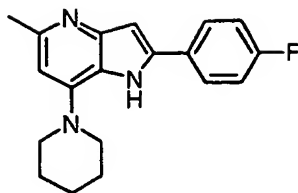
Example 231: 5-Methyl-7-piperidyl-2-(4-piperidylphenyl)furano[3,2-b]pyridine (31.0 mg, 0.08 mmol) was dissolved in EtOAc (5 mL) and heated to boiling. To the hot solution was added 1M ethereal HCl (0.20 mL, 0.20 mmol). The solution was left to cool to 25 °C. The resulting solid was collected by filtration, washed with EtOAc (2 x 2 mL), Et₂O (3 x 5 mL) and dried under vacuum at 25 °C to give 30 mg (6%) of the title compound as a brown colored solid. Mp: decomposition >170 °C. ¹H NMR (DMSO-d₆; 400 MHz): δ 1.54 (br s, 6), 1.64 (br s, 6), 2.43 (s, 3), 3.29 (br s, 4), 3.89 (br s, 4), 6.85 (s, 1), 7.10 (m, 1), 7.22 (s, 1), 7.80 (m, 2), 13.75 (s, 1). MS m/z : 376 (M+1 for free base). Anal. Calcd for C₂₄H₂₉N₃O•2HCl•2.5H₂O: C, 58.41; H, 7.35; N, 8.52; Cl, 14.37. Found C, 58.30; H, 7.28; N, 8.38; Cl, 14.18.

350

**Example 232****(a) 7-Chloro-5-methyl-2-(4-fluorophenyl)pyrrolo-[3,2-b]pyridine.**

5 To a solution of 3-amino-2,4-dichloro-6-methyl
pyridine (5.3 g, 28.2 mmol) in NEt₃ (190 mL), was added
(PPh₃)₂PdCl₂ (1.4 g, 2.1 mmol), and CuI (400 mg, 2.2
mmol). The mixture was cooled to 0 °C and a solution
of 4-fluorophenylacetylene (4.5 g, 37.5 mmol) in 10 mL
10 of DMF was added slowly via syringe. The mixture was
allowed to warm to room temperature then heated at 80
°C for 96 h. The mixture was allowed to cool to room
temperature and filtered through a short pad of celite.
The celite was rinsed with NEt₃ and the filtrate was
15 concentrated *in vacuo*. The crude material was purified
by flash chromatography on silica gel with 1:4
EtOAc:hexanes to afford 2.91 g (40%) of starting
material followed by 2.97 g (55%, 91% based on
recovered starting material) of 3-Amino-4-chloro-6-
20 methyl-2-(2-phenylethynyl)pyridine as a dark brown
solid. MS *m/z*: 243 (M+1). The crude intermediate (2.90
g, 11.1 mmol) was dissolved in anhydrous DMF (250 mL),
CuI (310 mg, 16.3 mmol) was added and the mixture was
heated at 95 °C for 19 h. The reaction mixture was
25 cooled to room temperature and the crude product was
collected by filtration. Chromatography on silica with
8:1 CHCl₃:MeOH gave 1.6 g (54%, 30% over two steps) of
7-chloro-5-methyl-2-(4-fluorophenyl)pyrrolo-[3,2-
b]pyridine. ¹H NMR (DMSO-*d*₆; 500 MHz): δ 2.50 (s, 3),
30 6.99 (s, 1), 7.11 (s, 1), 7.32 (t, 2, *J* = 8.8), 8.05 (m,
2), 11.78 (s, 1). MS *m/z*: 262 (M+H).

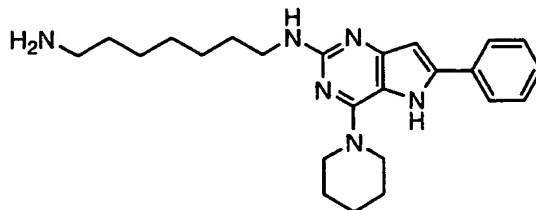
351



(b) 5-Methyl-2-(4-fluorophenyl)-7-piperidylpyrrolo[3,2-b]pyridine.

A mixture of 7-chloro-5-methyl-2-(4-fluorophenyl) pyrrolo[3,2-b]pyridine (1.5 g, 5.9 mmol) in 3:1 o-xylene/piperidine (20 mL) was heated at 140 °C in a Teflon-capped pressure tube for 5 d. The mixture was allowed to cool to room temperature, diluted with 5 mL of a 5:1 mixture of CHCl₃:MeOH and run through a short column of silica eluting with 10:1 CHCl₃:MeOH. The filtrate was concentrated in vacuo, the crude product was dissolved in 20 mL of CHCl₃ and 1M HCl in ether (8.0 mL, 8.0 mmol) was added slowly via syringe. The mixture was dried by rotary evaporation and triturated with a 1:5 mixture of EtOH:EtOAc. Filtration and drying under high vacuum for 24 h gave 1.45 g (70%) of the title compound as a yellow solid. ¹H NMR (DMSO-d₆; 500 MHz): δ 1.72 (b s, 6), 2.55 (s, 3), 3.76 (s, 4), 6.80 (s, 1), 6.89 (s, 1), 7.40 (t, 2, J = 8.8), 8.02 (m, 2), 11.82 (s, 1), 13.79 (s, 1). Anal. Calcd for C₁₉H₂₀FN₃•HCl•0.5H₂O: C, 64.31; H, 6.25; N, 11.84. Found: C, 63.95; H, 6.15; N, 12.21.

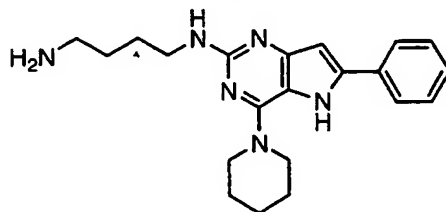
Example 233



(7-Aminoheptyl)-(6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidin-2-yl)amine Hydrochloride Hydrate.

To a sealed 5-mL vial was added 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 203(c)) (55 mg, 0.176 mmol), 1,7-diaminoheptane (Aldrich Chemical Company) (92 mg, 0.703 mmol) and pyridine (1.5 mL). The solution was heated at 150 °C for 3 h. The reaction mixture was allowed to cool to room temperature and pyridine was removed *in vacuo*. The resulting residue was washed with sat. NaHCO₃, and extracted with CHCl₃, three times. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography on silica gel with MeOH/CH₂Cl₂/NH₄OH(4:95:1) as eluant to afford 30mg (42%) of a light-brown solid. The free base (30 mg, 0.074 mmol) was dissolved in CH₂Cl₂ (2 mL) and anhydrous ethereal HCl (0.11mL of a 2 M soln, 0.22mmol) was added dropwise. The precipitate was collected by filtration, washed with EtOAc/ether (1:1) (3 x 1 mL) and dried over vacuum to give 25 mg (66 %) of the title compound as a light brown solid. ¹H NMR (DMSO-d₆;400 MHz): δ 1.30-1.20 (m, 16), 2.90-2.95 (m, 2), 3.55-3.60 (m, 2), 4.11 (s, 4), 6.83 (s, 1), 7.60-8.30 (m, 9). MS *m/z* : 407 (M+1). Anal. Calcd for C₂₄H₃₄N₆•3HCl•H₂O: C, 54.00; H, 7.36; N, 15.74. Found: C, 54.20; H, 7.02; N, 14.46.

25

Example 234

(4-Aminobutyl)-(6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidin-2-yl)amine Hydrochloride Hydrate.

30 To a sealed 3-mL vial was added 2-chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine (Example 203(c))

(56 mg, 0.18 mmol), 1,4-diaminobutane (Aldrich Chemical Company) (158 mg, 1.80 mmol) and pyridine (0.5 mL). The solution was heated at 150 °C for 6 h. The reaction mixture was allowed to cool to room temperature and pyridine was removed *in vacuo*. The resulting residue was washed with sat. NaHCO₃, and extracted with CHCl₃, three times. The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The resulting crude oil was purified by flash chromatography on silica gel with MeOH/CH₂Cl₂/NH₄OH (4:95:1) as eluant to afford 25 mg (38 %) of a light-brown solid. The free base (30 mg, 0.074 mmol) was dissolved in CH₂Cl₂ (2 mL) and anhydrous ethereal HCl (0.10 mL of a 2 M soln, 0.20 mmol) was added dropwise. The precipitate was collected by filtration, washed with EtOAc/ether (1:1) (3 x 0.5 mL) and dried over vacuum to give 25 mg (77 %) of the title compound as a light brown solid. ¹H NMR (MeOH-d₆; 400 MHz): δ 1.90-2.10 (m, 10), 3.20-3.20 (m, 2), 3.70-3.80 (m, 2), 4.20-4.30 (m, 4), 6.84 (s, 1), 7.70-8.20 (m, 5). MS *m/z*: 365 (M+1). Anal. Calcd for C₂₁H₂₈N₆•3HCl•H₂O: C, 51.28; H, 6.76; N, 17.08. Found: C, 52.00; H, 6.81; N, 15.01.

Biological Studies

Feeding Studies in Mice

Protocol For Icv Administration Of Compounds In Ad-Lib Fed OB/OB Female Mice.

Eight week old (approx. 50g) OB/OB female mice were obtained from Jackson Laboratories (Bar Harbor, ME) and given one week to acclimate to the animal facility before the experiment. Animals were housed 10 per cage and were provided with food and water ad-lib. Immediately prior to injection, animals were removed from group housing and lightly anesthetized using 4%

isofluorane vapor. Freehand intracerebroventricular ("icv") injection of compounds was done in a 100% DMSO vehicle in a volume of 5 μ l. Immediately following the injection, animals were placed in individual cages and were provided with a pre-weighed portion of regular chow pellets. Total amount of food consumed was measured at 1, 2, 4 and 24 hours post-injection:

The results show a statistically significant decrease in food intake in obese animals:

<u>I.C.V. treatment</u>	<u>4 hr food intake (g \pm S.E.M.)</u>
vehicle	0.61 \pm 0.10
Example 35	0.29 \pm 0.11*

*significantly different from vehicle, $p < 0.05$

Protocol for mice studies

Protocol For IP Administration Of Compounds In Male BALB-C Mice.

Male BALB-C mice (20-25 g) were obtained from Charles Rivers (Wilmington, MA) and were given at least a one week acclimation period to Amgen's animal care facilities. Animals were housed 10/cage and were provided ad libitum food and water. For testing, mice were fasted for 18-20 hr (overnight) prior to the start of the experiment. On the day of the experiment, mice were removed from group housing and placed into individual cages (without food). Test compounds or vehicle was then administered via the intraperitoneal (i.p.) route of administration. Test compounds were suspended in a 2% tween solution; the 2% tween solution was used as the vehicle treatment (control group). Group sizes for each treatment were 6-8 animals. After 30 min, premeasured food was placed into the cages. Two hours later, the food was weighed again. The difference between 2 hr weight and the premeasured weight was taken as 2 hr food intake. The following

compounds showed at least a 10% inhibition of feeding in the mouse model at 30 mg/kg (ip): Examples 9, 30, 32, 33, 35, 61, 63, 64, 65, 66e, 68c, 69c, 71e, 72, 73a, 76c, 77, 80d, 81d, 85, 92d, 93, 95c, 96, 97, 98, 101, 103, 107, 108, 111, 114, 116, 118, 119, 121, 122, 123, 124, 125, 130, 131, 194, 195d, 196c, 197, 198, 199, 215, 217, 218 and 232b.

Feeding Studies in Rats

10 Protocol For Icv Administration Of Compounds In Food-Deprived Long-Evans Male Rats

Adult male Long-Evans rats (approx. 275g) were obtained from Charles River Laboratories (Wilmington, MA) and given one week to acclimate to the animal facility. Animals were housed individually and given ad-lib access to food and water. After acclimation, animals were anesthetized (75 mg/kg Sodium Nembutal) and implanted with 23g cannulas (Plastics One, Roanoke, VA) into the right lateral cerebral ventricle. All animals were given at least 1 week post-operative recover before any experiment.

Animals were food deprived for 16 hours prior to injections. Intracerebroventricular injection of compounds was done in awake, unrestrained animals in a DMSO vehicle in a volume of 20 μ l. Immediately following the injection, the animals were returned to their home cage and were provided with a pre-weighed portion of regular rat chow pellets. Total food consumed was measured at 2 and 4 hours post-injection.

30 The results show a statistically significant decrease in food intake in food deprived animals:

<u>I.C.V. treatment</u>	<u>4 hr food intake (g \pm S.E.M.)</u>
vehicle	8.69 \pm 0.53
Example 1f	5.13 \pm 1.40*

*significantly different from vehicle, $p < 0.05$

Protocol For Icv Administration Of NPY Antagonists
Against pNPY Induced Feeding In Satiated Long-Evans
Male Rats

5 Adult male Long-Evans rats (approx. 275g) were
obtained from Charles River Laboratories (Wilmington,
MA) and given one week to acclimate to the animal
facility. Animals were housed individually and given
ad-lib access to food and water. After acclimation,
10 animals were anesthetized (75 mg/kg Sodium Nembutal)
and implanted with 23g cannulas (Plastics One, Roanoke,
VA) into the right lateral cerebral ventricle. All
animals were given at least 1 week post-operative
recover before any experiment.

15 Approximately 16 hours prior to injection, animals
were provided with access to 30 grams of a
sucrose/condensed milk/rat chow mash along with their
regular chow. Ninety minutes prior to injections,
regular chow was removed from the cages and animals
20 were provided with a fresh portion of the high sucrose
mash. Intracerebroventricular injection of antagonist
or vehicle was done in awake, unrestrained animals in a
DMSO vehicle in a volume of 20 μ l. Approximately 15
minutes after the administration of the antagonist or
25 vehicle, animals were given a second 5 μ l injection of
either water or pNPY. After the second injection, the
portion of high sucrose mash was weighed and total food
consumed was measured at 2 and 4 hours post-injection.

30 The results show the ability of the compounds of
the invention to significantly inhibit NPY induced
feeding behavior in animals:

<u>I.C.V. treatment</u>	<u>4 hr food intake ($\alpha \pm$ S.E.M.)</u>
vehicle	5.29 \pm 0.97
Example 2	3.35 \pm 0.62*

*significantly different from vehicle, $p < 0.05$

Protocol For IP Administration Of Compounds In Fasted
Long-Evans Male Rats

Male Long Evans rats (85-100 g) were obtained from
5 Harlan (Indianapolis, IN) and were given at least a one
week acclimation period to Ambients animal care
facilities. Animals were individually housed and were
provided ad libitum food and water. For testing, rats
were fasted for 18-20 hr (overnight) prior to the start
10 of the experiment. On the test day, test compounds or
vehicle was administered via the intraperitoneal (i.p.)
route of administration. Test compounds were suspended
in a 2% tween solution; the 2% tween solution was used
as the vehicle treatment (control group). Group sizes
15 for each treatment were 6-8 animals. After 30 min,
premeasured food was placed into the cages. Two hours
later, the food was weighed again. The difference
between 2 hr weight and the premeasured weight was
taken as 2 hr food intake. The following compounds
20 showed at least a 10% inhibition of feeding in the
mouse model at 30 mg/kg (ip): Examples 32, 33, 35, 61,
63, 65, 66e, 68c, 69c, 70e, 71e, 72, 76c, 80d, 85, 90,
95c, 96, 97, 101, 102, 104, 108, 111, 116, 118, 119,
121, 122, 123, 124, 126, 127, 134, 137, 141, 142, 143,
25 148, 150, 160, 168, 194, 195, 196c, 197d, 198, 200d,
202, 203, 209c, 216c, 217 and 232b.

Protocol For MCP-1 Inhibition Assay

Compounds of this invention may be shown to
30 inhibit monocyte chemoattractant protein 1 (MCP-1)
binding using the methods described in WO 98/06703
(incorporated herein by reference in its entirety).
Membranes for use the MCP-1 inhibition assay can be
prepared as follows. Human monocytic leukemia cell
35 line, THP-1, cells are centrifuged, washed twice in
ice-cold PBS (phosphate-buffered saline), resuspended

in ice-cold lysis buffer (5mM HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid)), pH 7.5, 2 mM EDTA, 5 ug/mL leupeptin, 5 ug/mL aprotinin, 5 ug/mL chymostatin and 100 ug/mL phenylmethanesulfonyl fluoride) at a concentration of about 5×10^7 cells/mL. The cell suspension is dounced 10-15 times using a B pestle (e.g., small pestle tissue grinder of 0.07 mm clearance) on ice. Nuclei and debris are removed by centrifugation at 500-1000 x g for about 10 minutes at about 4°C. The supernatant is transferred to a fresh tube and centrifuged at 25,000 x g for about 30 minutes at about 4°C. The supernatant is aspirated and the pellet is resuspended in buffer (10mM HEPES, pH 7.5, 300 mM sucrose, 1 ug/mL leupeptin, 1 ug/mL aprotinin, 1 ug/mL chymostatin and 10 ug/mL phenylmethanesulfonyl fluoride) using a minihomogenizer until all clumps are resolved. Membranes are aliquoted and frozen at about -70°C until needed. The total membrane protein can be determined with a standard protein assay, such as Bradford protein assay, BioRad, Richmond, CA.

Assays typically involve mixing about 10-20 ug of total membrane protein, a test compound in DMSO and about 0.2 nM I^{125} -labeled MCP-1 (Amersham, Arlington Heights, IL) in assay buffer (10 mM HEPES, pH 7.2, 1 mM $CaCl_2$, 5 mM $MgCl_2$, and 0.5% BSA) at a final volume of about 100 μ l. After about 30-60 minutes at room temperature, the assay is filtered with GF/C filters (Whatman glass fiber filters, Type C) or GF/B unifier plates (Packard) pre-soaked in 0.3% polyethyleneimine and washed twice with assay buffer containing about 0.5 M NaCl. The filters are dried and counted in a scintillation counter using standard scintillation fluid. Typically, the final concentration of compound in the assay ranges from about 0.05 μ M to about 100 μ M. Negative controls contain the same concentration of

DMSO present in assays containing compound. Positive controls contain about 250-500 nM cold MCP-1 (Peprotech, Rocky Hill, NJ) in DMSO. IC50 values can be calculated for each compound using a non-linear 3-parameter logistic curve fit. Any observed non-specific binding is subtracted from all data prior to analysis.

10 Protocols For CRF Antagonist and CRH Binding Protein Inhibition Activity Determination

Compounds of this invention may be shown to antagonize CRF and/or inhibit binding of CRH binding protein using the methods described in WO 98/05661, WO 98/08846 and WO 98/08847 (each of which is incorporated herein by reference in its entirety).

Protocol For Corticotropin Releasing Factor Antagonist Activity Determination

Compounds of this invention may be shown to be antagonists of CRF activity using the methods described in Endocrinology 116:1653-1659 (1985) and Peptides 10:179-188 (1985) (each of which are incorporated herein by reference in their entirety).

25 Protocol For Corticotropin Releasing Factor Hormone Binding Protein Inhibition Activity Determination

Compounds of this invention may be shown to inhibit CRH binding protein activity using the methods described in Brain Research 745:248-255 (1997) (incorporated herein by reference in its entirety).

Protocols For Protein Kinase Inhibition Activity Determination

Compounds of this invention may be shown to inhibit protein kinases and cell growth using the

methods described in WO 98/07726 (incorporated herein by reference in its entirety).

Protocols For EGF-R-PTK Inhibition Activity

5 Determination

- The inhibition of EGF-receptor-specific protein tyrosine kinase (EGF-R-PTK) can be demonstrated using the recombinant intracellular domain of the EGF receptor described in E. McGlynn et al., Europ. J. Biochem. 207:265-275 (1992). Inhibition of EGF-stimulated cellular tyrosine phosphorylation in the EGF-receptor can be shown in the human A431 epithelial carcinoma cell line by means of an ELISA which is described in U. Trinks et al., J. Med. Chem. 37:7, 1015-1027 (1994). U. Trinks et al. also describe a method for testing the inhibition EGF stimulation of quiescent BALB/c3T3 cells to rapidly induce the expression of c-fos mRNA which involves pretreating the cells with test compound
- 20 A method (Meyer et al., Int. J. Cancer 43:851 (1989)) for screening compounds for inhibition of the cell growth of EGF-dependent cell lines, such as the epidermoid BALB/c mouse keratinocyte cell line (Weissmann, and Aaronson, Cell 32:599 (1983)), the A431
- 25 cell line, a standard source of EGF-dependent epithelial cells (Carpenter and Zendegei, J. Anal. Biochem. 153:279-282 (1985)) and the like, is as follows: BALB/MK cells (about 10,000/microtitre plate well) are transferred to 96-well microtitre plates. A
- 30 test compound (dissolved in DMSO) is added in a dilution series of concentrations such that the final concentration of DMSO does not exceed 1% (v/v). The plates are incubated for about three days during which the control cultures without test compound are able to
- 35 undergo at least three cell-division cycles. The growth of the MK cells is measured by means of

Methylene Blue staining (the cells are fixed with glutaraldehyde, washed with water and stained with 0.05% Methylene Blue). After washing, the stain is eluted with 3% HCl and the optical density per well of the microtitre plate is measured, such as with a Titertek Multiscan, at 665 nm. The IC_{50} of the test compound is calculated based on the cell counts.

A method for in vivo screening of compounds for inhibition of the growth of tumour cells, such as the human epidermoid carcinoma A431 (ATCC No. CRL 1555; American Type Culture Collection, Rockville, Maryland, USA; Santon et al., Cancer Research 46:4701-4705 (1986); and Ozawa et al., Int. J. Cancer 40:706-710 (1987)) is as follows. The human epidermoid carcinoma A431 is transplanted into female BALB/c nude mice (Bomholtgard, Denmark). This carcinoma has been reported to exhibit a growth that correlates with the extent of the expression of the EGF-receptor. Tumours having a volume of approximately 1 cm³ cultured in vivo are surgically removed from experimental animals under sterile conditions. These tumours are comminuted and suspended in 10 volumes (w/v) of phosphate-buffered saline. The suspension is injected s.c. (0.2 ml/mouse in phosphate-buffered saline) into the left flank of the animals. Alternatively, 1 x 10⁶ cells from an in vitro culture in 0.2 ml of phosphate-buffered saline can be injected. Treatment with a test compound is started 5 or 7 days after transplantation, when the tumours have reached a diameter of 4-5 mm. The test compound is administered, at different doses for different animal groups, once a day for 15 successive days. The tumour growth is determined by measuring the diameter of the tumours along three axes that are perpendicular to each other. The tumour volumes can be calculated using the formula $p \times L \times D^2/6$ (Evans et al., Brit. J. Cancer 45:466-8 (1982)).

Protocols For Determination of Activity Inhibition of
Other Protein Kinases

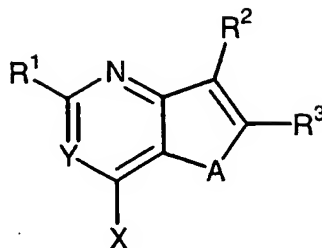
Methods for screening compounds for inhibition of
5 other protein tyrosine kinases that are involved in
signal transmission mediated by trophic factors, for
example abl kinase (v-abl kinase), kinases from the
family of the src kinases (c-src kinase and c-erbB2
kinase (HER-2)), and serine/threonine kinases (protein
10 kinase C), all of which are involved in growth
regulation and transformation in mammalian cells,
including human cells, are as follows. Inhibition of
v-abl tyrosine can be determined using [Val⁵]-
angiotensin II and [γ -³²P]-ATP substrates in the methods
15 of Lydon et al. (Oncogene Research 5:161-173 (1990))
and Geissler et al. (Cancer Research 52:4492-4498
(1992)). The inhibition of c-erbB2 tyrosine kinase
(HER-2) can be determined using an analogous method to
the above described EGF-R-TPK method (House et al.,
20 Europ. J. Biochem. 140:363-367 (1984)). Alternatively,
the activity of isolated c-erbB2 kinase can be
determined (Akiyama et al., Science 232:1644 (1986)).

The foregoing is merely illustrative of the
invention and is not intended to limit the invention to
25 the disclosed compounds. Variations and changes which
are obvious to one skilled in the art are intended to
be within the scope and nature of the invention which
are defined in the appended claims.

From the foregoing description, one skilled in the
30 art can easily ascertain the essential characteristics
of this invention, and without departing from the
spirit and scope thereof, can make various changes and
modifications of the invention to adapt it to various
usages and conditions.

We Claim:

1. A compound of formula



5 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or C(R⁶); A is N-H, N-R⁴ or CR⁴R⁷;

R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy,
 10 aryl, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂,
 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl or -Z(Q) radical;

R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
 15 -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
 -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
 -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
 -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical;

20 R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
 -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
 -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
 -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
 25 -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical,
 provided that R² is not an optionally substituted
 phenyl, pyridyl, pyrazinyl, pyrimidyl or pyridazinyl
 radical;

30 R³ is a (C₃-C₁₀)cycloalkyl, (C₁-C₈)alkyl,
 -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-,

- $-(C_1-C_8)alkyl)N(R^5)_2$, $-(C_1-C_8)alkyl)S(O)_p(C_1-C_8)alkyl)$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$,
5 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$,
10 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_mS(O)_pR^5$, $-D'(S(O)_qR^5)$,
 $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$,
 $-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^5SO_2R^5)$, $-D'(CON(R^5)_2)$,
 $-D'(CO_2R^5)$, $-D'(NR^5CON(R^5)_2)$, $-D'(NR^5(CO)R^5)$, $-D'(NR^5CO_2R^5)$,
15 $-D'(COR^5)$, $-D'(Q)$, $-D(aryloxy)$, $-D(aryl)$,
 $-D(heteroaryl)$, $-D((C_3-C_{10})cycloalkyl)$, $-D(NR^5SO_2R^5)$,
 $-D(CON(R^5)_2)$, $-D(CO_2R^5)$, $-D(S(O)_qR^5)$, $-D(NR^5CON(R^5)_2)$,
 $-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$, $-D(COR^5)$ or $-(NR^5)_k-D-Q$
radical;
- 20 R^4 is a $(C_1-C_8)alkyl$, $(C_3-C_{10})cycloalkyl$,
 $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$,
 $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$,
 $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$,
25 $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$
radical;
- X is a $(C_1-C_8)alkyl$, $(C_3-C_{10})cycloalkyl$,
 $-(NR^5)_k((C_1-C_8)alkyl)(C_1-C_8)alkoxy$,
30 $-(NR^5)_k((C_1-C_8)alkyl)aryloxy$, $-(NR^5)_k((C_1-C_8)alkyl)_kS(O)_pR^5$,
 $-(NR^5)_k((C_1-C_8)alkyl)S(O)_pR^5$, $-(NR^5)_kD(C_1-C_8)alkoxy$,
 $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
 $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
 $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
35 $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,
 $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,

365

- (NR⁵)_k(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_naryloxy, -Z(S(O)_qR⁵),
 -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl),
 -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂),
 -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵) or
 5 -Z(Q) radical; or

- X and A together with the adjoining carbon atoms form a
 5-membered to 10-membered mono- or bicyclic carbocyclic
 or heterocyclic ring which is optionally substituted
 10 with 1-2 radicals of R⁸;

- Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R⁸; wherein each R⁸ is independently a -OH,
 15 halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, -NH₂, -NH((C₁-C₈)alkyl),
 -N((C₁-C₈)alkyl)₂, or (C₁-C₈)alkyl radical;

- each R⁵ and R⁷ are each independently a hydrogen, -OH,
 (C₁-C₈)alkoxy, aryl, -NH₂, -NH((C₁-C₈)alkyl),
 20 -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl or (C₃-C₁₀)cycloalkyl
 radical;

- D is -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_n- and D' is
 -((C₁-C₈)alkyl)_k-;
 25

Z is D(NR⁵)_k, D'(NR⁵)_k, (NR⁵)_kD or (NR⁵)_kD';

- each k is independently 0 or 1;
 each m is independently an integer between 0 and 6;
 30 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and

- wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q,
 alkoxy or aryloxy moiety of any of X, R¹, R², R³, R⁴, R⁵,
 35 R⁶, R⁷ and R⁸ is optionally substituted with one or more
 radicals of halo, -CF₃, -OCF₃, -Z(COOH), -Z(OH),

- Z(NO₂), -Z(SH), -(C₁-C₈)alkyl, -(C₁-C₈)acyloxy,
 -(C₃-C₁₀)cycloalkyl, -S-((C₁-C₈)alkyl)_k-aryl,
 -((C₁-C₈)alkyl)_k-SO₂NH-aryl, -S-(C₁-C₈)alkyl,
 -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl);
- 5 -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁹SO₂R⁹),
 -Z(CON(R⁹)₂), -Z(CO₂R⁹), -Z(N(R⁹)₂), -Z(NR⁹CON(R⁹)₂),
 -Z(NR⁹(CO)R⁹), -Z(NR⁹CO₂R⁹), -Z(COR⁹), -Z(S(O)_pR⁹) or
 -Z(Q), wherein each R⁹ is independently a hydrogen or
 (C₁-C₈)alkyl radical and wherein such aryl, heteroaryl,
 10 cycloalkyl and Q substituents are optionally
 substituted with one or more radicals of halo, -NO₂,
 -CF₃, -OCF₃, -N(R⁹)₂, -C(O)R⁹, -CO₂R⁹, -OR⁹, -SR⁹ or
 (C₁-C₈)alkyl; and
- 15 provided that the total number of aryl, heteroaryl,
 cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹,
 R² and R³ is 0-4; and
- provided that:
- 20 (a) when A is NH, Y is N, R¹ is H, methyl or phenyl,
 and R³ is methyl, ethyl or phenyl, then (1) when R² is
 H, X is not -NH₂, -N(CH₂CH₃)₂, -NHCH₂CH₂N(CH₂CH₃)₂,
 -NHCH₂CH₂CH₂CO₂H, -NHCH₂CH₂OH, -NH-phenyl,
 -NHCH₂CH₂-phenyl, -NH-CH(CH₃)CH₂-phenyl,
 25 -NH-(methoxyphenyl), -NHCH₂CH₂-(dimethoxyphenyl),
 -NHCH₂CH₂-imidazolyl, -NHCH₂CH₂-(methylthioimidazolyl),
 -NHCH₂CH₂-cyclohexyl, -NH-cyclohexyl, piperidinyl,
 morpholinyl, -NHNH₂, -NHCH(CH₃)₂, -NH-butyl, -NH-
 CH(CH₃)(CH₂)₄CH₃, -NH(CH₂)₂cyclohexenyl, -NH-(CH₂)₅CH₃,
 30 -NHCH₂CH=CH₂, -NH-CH₂-phenyl, 4-methylpiperazine,
 -NHSO₂(4-aminophenyl) or -NH-(4-methylpiperazine); (2)
 when R² is -CH₂N(CH₂CH₃)₂, -CH₂NH-butyl,
 -CH₂NHCH₂CH₂-cyclohexenyl or -CH₂NHCH₂CH₂COOH, X is not
 -NH(CH₂)₂cyclohexenyl; and (3) when R² is methyl, acetyl
 35 or -COOCH₂CH₃, X is not -NH₂ or -NH(C(O)CH₃);

- (b) when R^1 is ethoxy, R^2 is H, R^3 is $-\text{COOCH}_2\text{CH}_3$, A is NH and Y is N, then X is not $-\text{NH}_2$;
- (c) when A is N-H or $\text{N}-\text{R}^4$, Y is C-H and R^1 is hydrogen, halo, alkyl, cycloalkyl, alkoxy or alkylthio, then (1) 5 when R^3 is methyl and R^2 is acetyl or $-\text{COOCH}_3$, X is not NH_2 or trifluoromethylphenyl; (2) when R^3 is methyl or $-\text{COOCH}_2\text{CH}_3$ and R^2 is H, X is not methyl; and (3) when one of R^2 , R^3 or R^4 is optionally substituted -ethyl- $\text{NR}^5\text{CONHR}^5$, X is not alkyl or cycloalkyl;
- 10 (d) when A is $\text{N}-\text{R}^4$ and Y is C-H, then R^3 is not $-\text{CO}_2\text{R}^5$;
- (e) when A is $\text{N}-\text{C}_1-\text{C}_6$ alkyl, Y is C-H or N, R^1 and R^3 are hydrogen, halo, alkyl, alkoxy or alkylthio, then R^2 is not thienyl optionally substituted with 1-3 halo, hydroxy, alkyl or alkoxy radicals;
- 15 (f) when A is CH_2 , Y is C-H, R^1 is NH_2 , R^3 is methyl and X is methyl, then R^2 is not $\text{C}(\text{O})\text{NH}_2$;
- (g) when A is N-H or $\text{N}-\text{R}^4$ and R^3 is aryl or heteroaryl, then R^2 is not aryl or heteroaryl;
- (h) when A is $\text{N}-\text{R}^4$, Y is N, R^1 is H and R^3 is alkyl, 20 then X is not $-\text{NH}_2$; and
- (i) when A is N-H or $\text{N}-\text{R}^4$ and R^2 is H, then R^3 is not optionally substituted phenyl which is substituted by $-\text{N}(\text{R}^5)-(\text{C}_2-\text{C}_6 \text{ alkyl})-\text{N}(\text{R}^5)_2$ or $-\text{N}(\text{R}^5)-(\text{C}_2-\text{C}_6 \text{ alkyl})-\text{Q}$.

25

2. The compound of claim 1 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or $\text{C}(\text{R}^6)$; A is N-H, $\text{N}-\text{R}^4$ or CR^4R^7 ;

- 30 R^6 is a hydrogen, -OH, halo, $-\text{CF}_3$, $-\text{OCF}_3$, $(\text{C}_1-\text{C}_8)\text{alkoxy}$, aryl, $-\text{NH}_2$, $-\text{NH}((\text{C}_1-\text{C}_8)\text{alkyl})$, $-\text{N}((\text{C}_1-\text{C}_8)\text{alkyl})_2$, $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_3-\text{C}_{10})\text{cycloalkyl}$ or $-\text{Z}(\text{Q})$ radical;

- R^1 is a hydrogen, halo, -OH, $-\text{NO}_2$, $-\text{NHOH}$, $-\text{CF}_3$, $-\text{OCF}_3$, 35 $(\text{C}_1-\text{C}_8)\text{alkyl}$, $(\text{C}_3-\text{C}_{10})\text{cycloalkyl}$, $-\text{Z}((\text{C}_1-\text{C}_8)\text{alkoxy})$, $-\text{Z}(\text{aryloxy})$, $-\text{Z}(\text{aryl})$, $-\text{Z}(\text{heteroaryl})$,

-Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
 -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
 -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical,
 provided R¹ is not an optionally substituted aryl or
 5 heteroaryl radical;

R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
 -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
 10 -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
 -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵),
 -Z(S(O)_pR⁵) or -Z(Q) radical, provided that R² is not an
 optionally substituted aryl or heteroaryl radical;

15 R³ is a (C₃-C₁₀)cycloalkyl, (C₃-C₈)alkyl,
 -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-,
 -((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl),
 -(CH₂)((C₃-C₁₀)cycloalkyl)_k(CH₂)_mOH,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH,
 20 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)OH,
 -(CH₂)((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)(C₁-C₈)alkoxy,
 -(CH₂)((C₃-C₁₀)cycloalkyl)_k(CH₂)_mN(R⁵)₂,
 25 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)N(R⁵)₂,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mS(O)_pR⁵,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(CO₂R⁵),
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(COR⁵),
 30 -((C₁-C₈)alkyl)(CO₂R⁵), -((C₁-C₈)alkyl)(COR⁵),
 -D'(S(O)_pR⁵), -D'(aryloxy), -D'(aryl), -D'(heteroaryl),
 -D'((C₃-C₁₀)cycloalkyl), -D'(NR⁵SO₂R⁵), -D'(CON(R⁵)₂),
 -D'(NR⁵CON(R⁵)₂), -D'(NR⁵(CO)R⁵), -D'(NR⁵CO₂R⁵), -D'(Q),
 -D(aryloxy), -D(aryl), -D(heteroaryl),
 35 -D((C₃-C₁₀)cycloalkyl), -D(NR⁵SO₂R⁵), -D(CON(R⁵)₂),

$-D(S(O)_pR^5)$, $-D(NR^5CON(R^5)_2)$, $-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$ or $-(NR^5)_k-D-Q$ radical, provided R^3 is not $-SO_2NH_2$;

R^4 is a (C_1-C_8) alkyl, (C_3-C_{10}) cycloalkyl,

- 5 $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$,
 $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$,
 $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$,
 $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$
 radical;

10

X is a $-(NR^5)_k((C_1-C_8)alkyl)(C_1-C_8)alkoxy$,
 $-(NR^5)_k((C_1-C_8)alkyl)aryloxy$, $-(NR^5)((C_1-C_8)alkyl)_kS(O)_pR^5$,
 $-(NR^5)_k((C_1-C_8)alkyl)S(O)_pR^5$, $-(NR^5)D(C_1-C_8)alkoxy$,
 $-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$,
 15 $-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
 $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
 $-(NR^5)(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)aryloxy$,
 $-(NR^5)_k(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_maryloxy$,
 $-(NR^5)_k(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_maryloxy$, $-Z(S(O)_pR^5)$,

20

$-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$,
 $-Z(NR^5SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$,
 $-Z(NR^5CON(R^5)_2)$, $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$ or
 $-Z(Q)$ radical; or

- 25 X and A together with the adjoining carbon atoms form a
 5-membered to 10-membered mono- or bicyclic carbocyclic
 or heterocyclic ring which is optionally substituted
 with 1-2 radicals of R^8 ;

- 30 Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R^8 ; wherein each R^8 is independently a $-OH$,
 halo, $-CF_3$, $-OCF_3$, $(C_1-C_8)alkoxy$, $-NH_2$, $-NH((C_1-C_8)alkyl)$,
 $-N((C_1-C_8)alkyl)_2$, or $(C_1-C_8)alkyl$ radical;

35

370

each R^5 and R^7 are each independently a hydrogen, -OH, (C_1-C_8) alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, $(C_1-C_8)alkyl$ or $(C_3-C_{10})cycloalkyl$ radical;

5

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_n$ and D' is $-((C_1-C_8)alkyl)_k$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

10

each k is independently 0 or 1;

each m is independently an integer between 0 and 6;

each p is independently an integer between 0 and 2; and

each q is independently 1 or 2; and

15

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$,

20

$-Z(NO_2)$, $-Z(SH)$, $-(C_1-C_8)alkyl$, $-(C_1-C_8)acyloxy$,

$-(C_3-C_{10})cycloalkyl$, $-S-((C_1-C_8)alkyl)_k-aryl$,

$-((C_1-C_8)alkyl)_k-SO_2NH-aryl$, $-S-(C_1-C_8)alkyl$,

$-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$,

$-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^9SO_2R^9)$,

25

$-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$,

$-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(O)_2R^9)$ or

$-Z(Q)$, wherein each R^9 is independently a hydrogen or $(C_1-C_8)alkyl$ radical and wherein such aryl, heteroaryl, cycloalkyl and Q substituents are optionally

30

substituted with 1-3 radicals of halo, $-NO_2$, $-CF_3$,

$-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or $(C_1-C_8)alkyl$.

3. The compound of claim 2 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is N-H, $N-R^4$ or CHR^4 ;

35

- R^1 is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₆)cycloalkyl, -Z((C₁-C₈)alkoxy),
 -Z((C₃-C₆)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(N(R⁵)₂) or -Z(Q)
 5 radical;
- R^2 is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
 -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
 10 -Z((C₃-C₁₀)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(CON(R⁵)₂),
 -Z(N(R⁵)₂), -Z(NR¹⁰CON(R⁵)₂), -Z(NR¹⁰(CO)R⁵), -Z(NR¹⁰CO₂R⁵),
 -Z(S(O)_pR⁵) or -Z(Q) radical, provided that R^2 is not an
 optionally substituted aryl or heteroaryl radical;
- 15 R^3 is a (C₃-C₁₀)cycloalkyl, (C₃-C₈)alkyl,
 -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-,
 -((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl),
 -(CH₂)((C₃-C₁₀)cycloalkyl)_x(CH₂)_mOH,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH,
 20 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_x(CH₂)OH,
 -(CH₂)((C₃-C₁₀)cycloalkyl)_x(CH₂)_m(C₁-C₈)alkoxy,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_x(CH₂)(C₁-C₈)alkoxy,
 -(CH₂)((C₃-C₁₀)cycloalkyl)_x(CH₂)_mN(R⁵)₂,
 25 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_x(CH₂)N(R⁵)₂,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mS(O)_pR⁵,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(CO₂R⁵),
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(COR⁵),
 30 -((C₁-C₈)alkyl)(CO₂R⁵), -((C₁-C₈)alkyl)(COR⁵),
 -D'(S(O)_pR⁵), -D'(aryloxy), -D'(aryl), -D'(heteroaryl),
 -D'((C₃-C₁₀)cycloalkyl), -D'(NR¹⁰SO₂R⁵), -D'(CON(R⁵)₂),
 -D'(NR¹⁰CON(R⁵)₂), -D'(NR¹⁰(CO)R⁵), -D'(NR¹⁰CO₂R⁵), -D'(Q),
 -D(aryloxy), -D(aryl), -D(heteroaryl),
 35 -D((C₃-C₁₀)cycloalkyl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂),

372

$-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$
or $-(NR^{10})_x-D-Q$ radical, provided R^3 is not $-SO_2NH_2$;

R^4 is a (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, $-N(R^5)_2$ or $-Z(Q)$
5 radical;

X is a $-(NR^{10})((C_1-C_8)$ alkyl) (C_1-C_8) alkoxy,
 $-(NR^{10})((C_1-C_8)$ alkyl)aryloxy, $-(NR^{10})S(O)_pR^5$,
 $-(NR^{10})((C_1-C_8)$ alkyl) $S(O)_pR^5$, $-(NR^{10})D(C_1-C_8)$ alkoxy,
10 $-(NR^{10})(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)(C_1-C_8)$ alkoxy,
 $-(NR^{10})(CH_2)((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(NR^{10})(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(NR^{10})(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)$ aryloxy,
 $-(NR^{10})(CH_2)((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m$ aryloxy,
15 $-(NR^{10})(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m$ aryloxy,
 $-(NR^{10})D(S(O)_qR^5)$, $-(NR^{10})D'(S(O)_qR^5)$, $-(NR^{10})D(aryl)$,
 $-(NR^{10})D'(aryl)$, $-(NR^{10})D(heteroaryl)$,
 $-(NR^{10})D'(heteroaryl)$, $-(NR^{10})D((C_3-C_{10})$ cycloalkyl),
 $-(NR^{10})D'((C_3-C_{10})$ cycloalkyl), $-(NR^{10})D(NR^{10}SO_2R^5)$,
20 $-(NR^{10})D'(NR^{10}SO_2R^5)$, $-(NR^{10})D(CON(R^5)_2)$, $-(NR^{10})D'(CON(R^5)_2)$,
 $-(NR^{10})D(CO_2R^5)$, $-(NR^{10})D'(CO_2R^5)$, $-(NR^{10})D(N(R^5)_2)$, $-N(R^5)_2$,
 $-(NR^{10})D'(N(R^5)_2)$, $-(NR^{10})D(NR^{10}CON(R^5)_2)$,
 $-(NR^{10})D'(NR^{10}CON(R^5)_2)$, $-(NR^{10})D(NR^{10}(CO)R^5)$,
 $-(NR^{10})D'(NR^{10}(CO)R^5)$, $-(NR^{10})D(NR^{10}CO_2R^5)$,
25 $-(NR^{10})D'(NR^{10}CO_2R^5)$, $-(NR^{10})D(COR^5)$, $-(NR^{10})D'(COR^5)$,
 $-(NR^{10})D-Q$, $-(NR^{10})D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or
 (C_1-C_4) alkyl radical; or

30

X and A together with the adjoining carbon atoms form a
5-membered to 10-membered mono- or bicyclic
heterocyclic ring which is optionally substituted with
1-2 radicals of R^8 ;

35

373

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8 ; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$,
 5 $-N((C_1-C_4)alkyl)_2$, or $(C_1-C_4)alkyl$ radical;

each R^5 is independently a hydrogen, -OH, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, $(C_1-C_4)alkyl$ or $(C_3-C_6)cycloalkyl$ radical;

10

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

15

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;

each m is independently an integer between 0 and 4;

each p is independently an integer between 0 and 2; and

each q is independently 1 or 2; and

20

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^4 and R^5 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)alkyl$,

25

$-(C_1-C_4)acyloxy$, $-(C_3-C_6)cycloalkyl$,
 $-S-((C_1-C_4)alkyl)_k-aryl$, $-((C_1-C_4)alkyl)_k-SO_2NH-aryl$,
 aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$,
 $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$,
 $-S(O)_2(C_1-C_4)alkyl$ or Q, wherein each R^9 is independently
 30 a hydrogen or $(C_1-C_4)alkyl$ radical and wherein such aryl, heteroaryl, cycloalkyl and Q substituents are optionally substituted with 1-2 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or $(C_1-C_4)alkyl$; and

35

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹, R² and R³ is 0-3.

5

4. The compound of claim 3 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is N-H or N-R⁴;

10 R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -(NR¹⁰)_x((C₁-C₂)alkyl)_k-cyclopropyl or -(NR¹⁰)_x((C₁-C₂)alkyl)_k-N(R¹⁰)₂ radical;

R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃,
15 (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, -(NR¹⁰)_x((C₁-C₂)alkyl)_k-(C₁-C₄)alkoxy, -(NR¹⁰)_x((C₁-C₂)alkyl)_k-(CON(R⁵))₂,
-(NR¹⁰)_x((C₁-C₂)alkyl)_k-(N(R⁵))₂, -(NR¹⁰)_x((C₁-C₂)alkyl)_k-(S(O)_pR⁵) or -(NR¹⁰)_x((C₁-C₂)alkyl)_k-Q radical;

20 R³ is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl, -(C₁-C₄)alkylOH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-,
-(C₁-C₄)alkylN(R⁵)₂, -(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_mOH,
-(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_mOH,
-(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_mOH,

25 -(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_m(C₁-C₄)alkoxy,
-(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_m(C₁-C₄)alkoxy,
-(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_m(C₁-C₄)alkoxy,
-(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_mN(R⁵)₂,
-(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_mN(R⁵)₂,

30 -(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_mN(R⁵)₂,
-(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_mS(O)_pR⁵,
-(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_m(CO₂R⁵),
-(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)_m(COR⁵), -D'(S(O)_qR⁵),
-D'(aryloxy), -D'(aryl), -D'(heteroaryl),

35 -D'((C₃-C₁₀)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl),
-D(heteroaryl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵))₂, -D(S(O)_qR⁵),

375

$-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-Q$ radical, provided R^3 is not $-SO_2NH_2$;

R^4 is a (C_1-C_4) alkyl radical;

5

X is a $-(N((C_1-C_4)alkyl))-(C_1-C_4)alkyl$ aryloxy,

$-(N((C_1-C_4)alkyl))-$

$(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$,

$-(N((C_1-C_4)alkyl))-$

10

$(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$,

$-(N((C_1-C_4)alkyl))-$

$(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$,

$-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)aryloxy$,

$-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_maryloxy$,

15

$-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_maryloxy$,

$-(N((C_1-C_4)alkyl))-D(aryl)$, $-(N((C_1-C_4)alkyl))-D'(aryl)$,

$-(N((C_1-C_4)alkyl))-D(heteroaryl)$, $-(N((C_1-C_4)alkyl))-$

$D'(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}SO_2R^5)$,

$-(N((C_1-C_4)alkyl))-D(CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-$

20

$D(CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(N(R^5)_2)$, $-N(R^5)_2$,

$-(N((C_1-C_4)alkyl))-D(NR^{10}CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-$

$D(NR^{10}(CO)R^5)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CO_2R^5)$,

$-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))-D-Q$,

$-(N((C_1-C_4)alkyl))-D'-Q$ or Q radical;

25

wherein each R^{10} is independently a hydrogen or

(C_1-C_4) alkyl radical; or

X and A together with the adjoining carbon atoms form a

30

5-membered to 10-membered mono- or bicyclic

heterocyclyl moiety which is optionally substituted

with 1-2 radicals of R^8 ;

Q is a 4-membered to 10-membered heterocyclyl or

35

heteroaryl ring optionally substituted with 1-2

radicals of R^8 ; wherein each R^8 is independently a $-OH$,

376

halo, $-\text{CF}_3$, $-\text{OCF}_3$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $-\text{NH}_2$, $-\text{NH}((\text{C}_1\text{-C}_4)\text{alkyl})$,
 $-\text{N}((\text{C}_1\text{-C}_4)\text{alkyl})_2$, or $(\text{C}_1\text{-C}_4)\text{alkyl radical}$;

each R^5 is independently a hydrogen, $-\text{OH}$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$,
5 $-\text{NH}_2$, $-\text{NH}((\text{C}_1\text{-C}_4)\text{alkyl})$, $-\text{N}((\text{C}_1\text{-C}_4)\text{alkyl})_2$ or $(\text{C}_1\text{-C}_4)\text{alkyl radical}$;

D is $-(\text{CH}_2)_m((\text{C}_3\text{-C}_6)\text{cycloalkyl})_k(\text{CH}_2)_m-$ and D' is
 $-(\text{C}_1\text{-C}_4)\text{alkyl})_k-$;

10

Z is $(\text{NR}^{10})_k\text{D}$ or $(\text{NR}^{10})_k\text{D}'$;

each k is independently 0 or 1;

each m is independently an integer between 0 and 3;

15 each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy
moiety of any of X, R^2 and R^3 is optionally substituted
20 with 1-2 radicals of halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{NO}_2$,
 $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{acyloxy}$, $-\text{NR}^9\text{SO}_2\text{R}^9$, $-\text{CON}(\text{R}^9)_2$, $-\text{CO}_2\text{R}^9$,
 $-\text{N}(\text{R}^9)_2$, $-\text{NR}^9\text{CON}(\text{R}^9)_2$, $-\text{NR}^9(\text{CO})\text{R}^9$, $-\text{NR}^9\text{CO}_2\text{R}^9$, $-\text{COR}^9$ or
 $-\text{S}(\text{O})_2(\text{C}_1\text{-C}_4)\text{alkyl}$, wherein each R^9 is independently a
hydrogen or $(\text{C}_1\text{-C}_4)\text{alkyl radical}$; and

25

provided that the total number of aryl, heteroaryl,
cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1 ,
 R^2 and R^3 is 1-3.

30

5. The compound of claim 4 or a pharmaceutically
acceptable salt, ester, solvate or N-oxide thereof,
wherein Y is N; A is N-H;

R^1 is a bromo, chloro, fluoro, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₂)alkyl, (C₁-C₂)alkoxy, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-cyclopropyl, -NH₂ or -NH((C₁-C₂)alkyl) radical;

- 5 R^2 is a hydrogen, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₂)alkyl or (C₁-C₂)alkoxy radical;

- R^3 is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl, -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-,
 10 -((C₁-C₄)alkyl)N(R⁵)₂, -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mOH, -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₂)alkoxy, -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(C₁-C₂)alkoxy,
 15 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₂)alkoxy, -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂, -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mN(R⁵)₂, -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂, -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mS(O)_pR⁵,
 20 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(CO₂R⁵), -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(COR⁵), -D'(S(O)_qR⁵), -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'((C₃-C₆)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂), -D(S(O)_qR⁵),
 25 -D(NR¹⁰CON(R⁵)₂), -D(NR¹⁰(CO)R⁵), -D(NR¹⁰CO₂R⁵) or -(NR¹⁰)_k-D-Q radical, provided R³ is not -SO₂NH₂;

- X is a -N((C₁-C₄)alkyl)₂ or 4-membered to 10-membered heterocyclyl or heteroaryl ring, having a nitrogen atom
 30 ring member bonded directly to the carbon atom adjoining X, optionally substituted with 1-2 radicals of R⁸;

- wherein each R¹⁰ is independently a hydrogen or
 35 (C₁-C₂)alkyl radical; or

X and A together with the adjoining carbon atoms form a 8-membered to 10-membered bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of
5 R⁸;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R⁸; wherein each R⁸ is independently a -OH;
10 halo, -CF₃, -OCF₃, (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl), -N((C₁-C₂)alkyl)₂, or (C₁-C₂)alkyl radical;

each R⁵ is independently a hydrogen, -OH, (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl), -N((C₁-C₂)alkyl)₂ or (C₁-C₂)alkyl
15 radical;

D is -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_m- and D' is -((C₁-C₄)alkyl)_k-;

20 Z is (NR¹⁰)_kD or (NR¹⁰)_kD';

each k is independently 0 or 1;
each m is independently an integer between 0 and 2;
each p is independently an integer between 0 and 2; and
25 each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R² and R³ is optionally substituted with 1-2 radicals of halo, -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂,
30 (C₁-C₄)alkyl, (C₁-C₄)acyloxy, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹, -N(R⁹)₂, -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹ or -S(O)₂(C₁-C₄)alkyl, wherein each R⁹ is independently a hydrogen or (C₁-C₂)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹, R² and R³ is 1-2.

5

6. The compound of claim 2 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is C(R⁶); A is N-H, N-R⁴ or CHR⁴;

10 R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl radical;

R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃,
15 (C₁-C₈)alkyl, (C₃-C₆)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z((C₃-C₆)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(N(R⁵)₂) or -Z(Q) radical;

R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃,
20 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(CON(R⁵)₂), -Z(N(R⁵)₂), -Z(NR¹⁰CON(R⁵)₂), -Z(NR¹⁰(CO)R⁵), -Z(NR¹⁰CO₂R⁵), -Z(S(O)_pR⁵) or -Z(Q) radical, provided that R² is not an
25 optionally substituted aryl or heteroaryl radical;

R³ is a (C₃-C₁₀)cycloalkyl, (C₃-C₈)alkyl,
-((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-,
-((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl),
30 -(CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mOH,
-(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH,
-(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)OH,
-(CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
-(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
35 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_k(C₁-C₈)alkoxy,
-(CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mN(R⁵)₂,

- $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_mN(R^5)_2,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_mN(R^5)_2,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_mS(O)_pR^5,$
 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_m(CO_2R^5),$
 5 $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_m(COR^5),$
 $-((C_1-C_8)\text{alkyl})(CO_2R^5), -((C_1-C_8)\text{alkyl})(COR^5),$
 $-D'(S(O)_qR^5), -D'(\text{aryloxy}), -D'(\text{aryl}), -D'(\text{heteroaryl}),$
 $-D'((C_3-C_{10})\text{cycloalkyl}), -D'(NR^{10}SO_2R^5), -D'(CON(R^5)_2),$
 $-D'(NR^{10}CON(R^5)_2), -D'(NR^{10}(CO)R^5), -D'(NR^{10}CO_2R^5), -D'(Q),$
 10 $-D(\text{aryloxy}), -D(\text{aryl}), -D(\text{heteroaryl}),$
 $-D((C_3-C_{10})\text{cycloalkyl}), -D(NR^{10}SO_2R^5), -D(CON(R^5)_2),$
 $-D(S(O)_qR^5), -D(NR^{10}CON(R^5)_2), -D(NR^{10}(CO)R^5), -D(NR^{10}CO_2R^5)$
 or $-(NR^{10})_x-D-Q$ radical, provided R^3 is not $-SO_2NH_2$;
- 15 R^4 is a $(C_1-C_4)\text{alkyl}$, $(C_3-C_6)\text{cycloalkyl}$, $-N(R^5)_2$ or $-Z(Q)$ radical;
- X is a $-(NR^{10})((C_1-C_8)\text{alkyl})(C_1-C_8)\text{alkoxy},$
 $-(NR^{10})((C_1-C_8)\text{alkyl})\text{aryloxy}, - (NR^{10})S(O)_pR^5,$
 20 $-(NR^{10})((C_1-C_8)\text{alkyl})S(O)_pR^5, - (NR^{10})D(C_1-C_8)\text{alkoxy},$
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_m(C_1-C_8)\text{alkoxy},$
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_m(C_1-C_8)\text{alkoxy},$
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_m(C_1-C_8)\text{alkoxy},$
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_m\text{aryloxy},$
 25 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_m\text{aryloxy},$
 $-(NR^{10})(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_m\text{aryloxy},$
 $-(NR^{10})D(S(O)_qR^5), - (NR^{10})D'(S(O)_qR^5), - (NR^{10})D(\text{aryl}),$
 $-(NR^{10})D'(\text{aryl}), - (NR^{10})D(\text{heteroaryl}),$
 $-(NR^{10})D'(\text{heteroaryl}), - (NR^{10})D((C_3-C_{10})\text{cycloalkyl}),$
 30 $-(NR^{10})D'((C_3-C_{10})\text{cycloalkyl}), - (NR^{10})D(NR^{10}SO_2R^5),$
 $-(NR^{10})D'(NR^{10}SO_2R^5), - (NR^{10})D(CON(R^5)_2), - (NR^{10})D'(CON(R^5)_2),$
 $-(NR^{10})D(CO_2R^5), - (NR^{10})D'(CO_2R^5), - (NR^{10})D(N(R^5)_2), -N(R^5)_2,$
 $-(NR^{10})D'(N(R^5)_2), - (NR^{10})D(NR^{10}CON(R^5)_2),$
 $-(NR^{10})D'(NR^{10}CON(R^5)_2), - (NR^{10})D(NR^{10}(CO)R^5),$
 35 $-(NR^{10})D'(NR^{10}(CO)R^5), - (NR^{10})D(NR^{10}CO_2R^5),$

381

- (NR¹⁰)D' (NR¹⁰CO₂R⁵); - (NR¹⁰)D(COR⁵), - (NR¹⁰)D' (COR⁵),
 - (NR¹⁰)D-Q, - (NR¹⁰)D'-Q or Q radical;

wherein each R¹⁰ is independently a hydrogen or
 5 (C₁-C₄)alkyl radical; or

X and A together with the adjoining carbon atoms form a
 5-membered to 10-membered mono- or bicyclic
 heterocyclic ring which is optionally substituted with
 10 1-2 radicals of R⁸;

Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R⁸; wherein each R⁸ is independently a -OH,
 15 halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl),
 -N((C₁-C₄)alkyl)₂, or (C₁-C₄)alkyl radical;

each R⁵ is independently a hydrogen, -OH, (C₁-C₄)alkoxy,
 -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂, (C₁-C₄)alkyl or
 20 (C₃-C₆)cycloalkyl radical;

D is -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_n- and D' is
 -((C₁-C₈)alkyl)_k-;

25 Z is D(NR¹⁰)_k, D'(NR¹⁰)_k, (NR¹⁰)_kD or (NR¹⁰)_kD';

each k is independently 0 or 1;
 each m is independently an integer between 0 and 4;
 each p is independently an integer between 0 and 2; and
 30 each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy
 moiety of any of X, R¹, R², R³, R⁴, R⁵ and R⁶ is
 optionally substituted with 1-3 radicals of halo and 1-
 35 2 radicals of -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂,
 -(C₁-C₄)alkyl, -(C₁-C₄)acyloxy, -(C₃-C₆)cycloalkyl,

-S-((C₁-C₄)alkyl)_k-aryl, -((C₁-C₄)alkyl)_k-SO₂NH-aryl,
 aryloxy, aryl, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹, -N(R⁹)₂,
 -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹,
 -S(O)₂(C₁-C₄)alkyl or Q, wherein each R⁹ is independently
 5 a hydrogen or (C₁-C₄)alkyl radical and wherein such
 aryl, heteroaryl, cycloalkyl and Q substituents are
 optionally substituted with 1-2 radicals of halo, -NO₂,
 -CF₃, -OCF₃, -N(R⁹)₂, -C(O)R⁹, -CO₂R⁹, -OR⁹, -SR⁹ or
 (C₁-C₄)alkyl; and

10 provided that the total number of aryl, heteroaryl,
 cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹,
 R² and R³ is 0-3.

15 7. The compound of claim 6 or a pharmaceutically
 acceptable salt, ester, solvate or N-oxide thereof,
 wherein Y is C(R⁶); A is N-H, N-R⁴;

20 R⁶ is a hydrogen, -OH, chloro, fluoro, -CF₃, -OCF₃,
 (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl), -N((C₁-C₂)alkyl)₂,
 or (C₁-C₄)alkyl radical;

R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃,
 25 (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-
 cyclopropyl or -(NR¹⁰)_k((C₁-C₂)alkyl)_k-N(R¹⁰)₂ radical;

R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃,
 (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-
 30 (C₁-C₄)alkoxy, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(CON(R⁵)₂),
 -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(N(R⁵)₂), -(NR¹⁰)_k((C₁-C₂)alkyl)_k-
 (S(O)_pR⁵) or -(NR¹⁰)_k((C₁-C₂)alkyl)_k-Q radical;

R³ is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl,
 35 -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-,
 -((C₁-C₄)alkyl)N(R⁵)₂, -(CH₂)((C₃-C₆)cycloalkyl)_k(CH₂)_mOH,

- (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m OH,
 - (CH₂)_m ((C₃-C₆) cycloalkyl)_k (CH₂) OH,
 - (CH₂) ((C₃-C₆) cycloalkyl)_k (CH₂)_m (C₁-C₄) alkoxy,
 - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m (C₁-C₄) alkoxy,
 - 5 - (CH₂)_m ((C₃-C₆) cycloalkyl)_k (CH₂) (C₁-C₄) alkoxy,
 - (CH₂) ((C₃-C₆) cycloalkyl)_k (CH₂)_m N(R⁵)₂,
 - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m N(R⁵)₂,
 - (CH₂)_m ((C₃-C₆) cycloalkyl)_k (CH₂) N(R⁵)₂,
 - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m S(O)_p R⁵,
 - 10 - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m (CO₂ R⁵),
 - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m (COR⁵), -D' (S(O)_q R⁵),
 - D' (aryloxy), -D' (aryl), -D' (heteroaryl),
 - D' ((C₃-C₁₀) cycloalkyl), -D' (Q), -D (aryloxy), -D (aryl),
 - D (heteroaryl), -D (NR¹⁰ SO₂ R⁵), -D (CON(R⁵)₂), -D (S(O)_q R⁵),
 - 15 -D (NR¹⁰ CON(R⁵)₂), -D (NR¹⁰ (CO) R⁵), -D (NR¹⁰ CO₂ R⁵) or - (NR¹⁰)_k -D-
- Q radical, provided R³ is not -SO₂ NH₂;

R⁴ is a (C₁-C₄) alkyl radical;

- 20 X is a - (N((C₁-C₄) alkyl)) - ((C₁-C₄) alkyl) aryloxy,
- (N((C₁-C₄) alkyl)) -
- (CH₂)_m ((C₃-C₆) cycloalkyl)_k (CH₂) (C₁-C₄) alkoxy,
- (N((C₁-C₄) alkyl)) -
- (CH₂) ((C₃-C₆) cycloalkyl)_k (CH₂)_m (C₁-C₄) alkoxy,
- 25 - (N((C₁-C₄) alkyl)) -
- (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m (C₁-C₄) alkoxy,
- (N((C₁-C₄) alkyl)) - (CH₂)_m ((C₃-C₆) cycloalkyl)_k (CH₂) aryloxy,
- (N((C₁-C₄) alkyl)) - (CH₂) ((C₃-C₆) cycloalkyl)_k (CH₂)_m aryloxy,
- (N((C₁-C₄) alkyl)) - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m aryloxy,
- 30 - (N((C₁-C₄) alkyl)) - D (aryl), - (N((C₁-C₄) alkyl)) - D' (aryl),
- (N((C₁-C₄) alkyl)) - D (heteroaryl), - (N((C₁-C₄) alkyl)) -
- D' (heteroaryl), - (N((C₁-C₄) alkyl)) - D (NR¹⁰ SO₂ R⁵),
- (N((C₁-C₄) alkyl)) - D (CON(R⁵)₂), - (N((C₁-C₄) alkyl)) -
- D (CO₂ R⁵), - (N((C₁-C₄) alkyl)) - D (N(R⁵)₂), - N(R⁵)₂,
- 35 - (N((C₁-C₄) alkyl)) - D (NR¹⁰ CON(R⁵)₂), - (N((C₁-C₄) alkyl)) -
- D (NR¹⁰ (CO) R⁵), - (N((C₁-C₄) alkyl)) - D (NR¹⁰ CO₂ R⁵),

- (N((C₁-C₄)alkyl)) - D(COR⁵), - (N((C₁-C₄)alkyl)) - D-Q,
 - (N((C₁-C₄)alkyl)) - D' - Q or Q radical;

wherein each R¹⁰ is independently a hydrogen or
 5 (C₁-C₄)alkyl radical; or

X and A together with the adjoining carbon atoms form a
 5-membered to 10-membered mono- or bicyclic
 heterocyclyl moiety which is optionally substituted
 10 with 1-2 radicals of R⁸;

Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R⁸; wherein each R⁸ is independently a -OH,
 15 halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl),
 -N((C₁-C₄)alkyl)₂, or (C₁-C₄)alkyl radical;

each R⁵ is independently a hydrogen, -OH, (C₁-C₄)alkoxy,
 -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂ or (C₁-C₄)alkyl
 20 radical;

D is -(CH₂)_n((C₃-C₆)cycloalkyl)_k(CH₂)_m- and D' is
 -((C₁-C₄)alkyl)_k-;

25 Z is (NR¹⁰)_kD or (NR¹⁰)_kD';

each k is independently 0 or 1;
 each m is independently an integer between 0 and 3;
 each p is independently an integer between 0 and 2; and
 30 each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy
 moiety of any of X, R², and R³ is optionally substituted
 with 1-2 radicals of halo, -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂,
 35 (C₁-C₄)alkyl, (C₁-C₄)acyloxy, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹,
 -N(R⁹)₂, -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹ or

-S(O)₂(C₁-C₄)alkyl, wherein each R⁹ is independently a hydrogen or (C₁-C₄)alkyl radical; and

provided that the total number of aryl, heteroaryl,
 5 cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹,
 R² and R³ is 1-3.

8. The compound of claim 7 or a pharmaceutically
 10 acceptable salt, ester, solvate or N-oxide thereof,
 wherein Y is C(R⁶); A is N-H;

R⁶ is a hydrogen, -OH, chloro, fluoro, -CF₃, -OCF₃,
 (C₁-C₂)alkoxy or (C₁-C₂)alkyl radical;

15

R¹ is a bromo, chloro, fluoro, -OH, -NO₂, -NHOH, -CF₃,
 -OCF₃, (C₁-C₂)alkyl, (C₁-C₂)alkoxy, -(NR¹⁰)_x((C₁-C₂)alkyl)_x-
 cyclopropyl, -NH₂ or -NH((C₁-C₂)alkyl) radical;

20 R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃,
 (C₁-C₂)alkyl or (C₁-C₂)alkoxy radical;

R³ is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl,
 -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-,
 25 -((C₁-C₄)alkyl)N(R⁵)₂, -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_mOH,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mOH,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_mOH,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₂)alkoxy,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(C₁-C₂)alkoxy,
 30 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₂)alkoxy,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mS(O)_pR⁵,
 35 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(CO₂R⁵),
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(COR⁵), -D'(S(O)_qR⁵),

-D' (aryloxy), -D' (aryl), -D' (heteroaryl),
 -D' ((C₃-C₆)cycloalkyl), -D' (Q), -D (aryloxy), -D (aryl),
 -D (heteroaryl), -D (NR¹⁰SO₂R⁵), -D (CON(R⁵)₂), -D (S(O)₂R⁵),
 -D (NR¹⁰CON(R⁵)₂), -D (NR¹⁰(CO)R⁵), -D (NR¹⁰CO₂R⁵) or -(NR¹⁰)_x-D-
 5 Q radical, provided R³ is not -SO₂NH₂;

X is a -N((C₁-C₄)alkyl)₂ or 4-membered to 10-membered
 heterocyclyl or heteroaryl ring, having a nitrogen atom
 ring member bonded directly to the carbon atom
 10 adjoining X, optionally substituted with 1-2 radicals
 of R⁸;

wherein each R¹⁰ is independently a hydrogen or
 (C₁-C₂)alkyl radical; or
 15

X and A together with the adjoining carbon atoms form a
 8-membered to 10-membered bicyclic heterocyclyl moiety
 which is optionally substituted with 1-2 radicals of
 R⁸;

20 Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R⁸; wherein each R⁸ is independently a -OH,
 halo, -CF₃, -OCF₃, (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl),
 25 -N((C₁-C₂)alkyl)₂, or (C₁-C₂)alkyl radical;

each R⁵ is independently a hydrogen, -OH, (C₁-C₂)alkoxy,
 -NH₂, -NH((C₁-C₂)alkyl), -N((C₁-C₂)alkyl)₂ or (C₁-C₂)alkyl
 radical;

30 D is -(CH₂)_m((C₅-C₆)cycloalkyl)_x(CH₂)_m- and D' is
 -((C₁-C₄)alkyl)_x-;

Z is (NR¹⁰)_xD or (NR¹⁰)_xD';
 35

each k is independently 0 or 1;
 each m is independently an integer between 0 and 2;
 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and

5

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R² and R³ is optionally substituted with 1-2 radicals of halo, -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂, (C₁-C₄)alkyl, (C₁-C₄)acyloxy, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹,
 10 -N(R⁹)₂, -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹ or -S(O)₂(C₁-C₄)alkyl, wherein each R⁹ is independently a hydrogen or (C₁-C₂)alkyl radical; and

provided that the total number of aryl, heteroaryl,
 15 cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹, R² and R³ is 1-2.

9. The compound of claim 1 which is:

20 2-Methyl-6-phenyl-4-(2-1,2,3,4-tetrahydroquinolino-2-yl)pyrrolo[3,2-d]pyrimidine;
 (S)-[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)pyrrolidin-2-yl]methan-1-ol;
 1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)
 25 pyrrolidin-3-ol;
 4-Homopiperidyl-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine;
 2-Methyl-6-phenyl-4-pyrrolidinylpyrrolo[3,2-d]pyrimidine;
 30 2-Methyl-6-(4-methylphenyl)-4-piperidylpyrrolo[3,2-d]pyrimidine;
 Dimethyl[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(4-piperidyl)]amine;
 Dimethyl{[1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(2-piperidyl)]methyl}amine;
 35 2-Isopropyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
 cis/trans-4-(3,5-dimethylpiperidinyl)-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine;

- [1-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-3-piperidyl]methan-1-ol;
2,5-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
- 5 2-(3-Hydroxyphenyl)-7-piperidylpyrrolo[3,2-b]pyridine;
7-Piperidyl-2-(2-pyridyl)pyrrolo[3,2-b]pyridine;
2-Cyclohex-1-enyl-7-piperidylpyrrolo[3,2-b]pyridine Hydrochloride;
2-Cyclohexyl-7-piperidylpyrrolo[3,2-b]pyridine;
- 10 2-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)thiophene;
2-Methyl-6-phenyl-4-(3-pyridinyl)pyrrolo[3,2-d]pyrimidine;
- 15 2-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-1,3-thiazole;
2-Methyl-4-(2-methylpyrrolidin-1-yl)-6-phenylpyrrolo[3,2-d]pyrimidine;
2-Methyl-6-phenyl-4-(pyrrolinyl)pyrrolo[3,2-d]pyrimidine;
- 20 2-Methyl-6-phenyl-4-(2-piperidineethanolyl)pyrrolo[3,2-d]pyrimidine;
2-Methyl-6-phenyl-4-(2-methylpiperidinyl)pyrrolo[3,2-d]pyrimidine;
- 25 2-Methyl-6-phenyl-4-(2-ethylpiperidinyl)pyrrolo[3,2-d]pyrimidine;
2-Methyl-6-phenyl-4-(1,2,3,6-tetrahydropyridinyl)pyrrolo[3,2-d]pyrimidine;
6-Phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-ylamine;
- 30 2-Methylthio-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
2-Ethyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
2-Cyclopropyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
- 35 6-(3-Chlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
4-Methoxy-1-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzene;
4-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenol;
- 40 6-(4-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
4-Azetidinyl-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine;

- 2-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)
thiophene;
- 2-Methyl-4-piperidyl-6-(2-pyridyl)pyrrolo[3,2-d]
pyrimidine;
- 5 6-Adamantanyl-2-methyl-4-piperidylpyrrolo[3,2-d]
pyrimidine;
- 2-Methyl-4-piperidyl-6-pyrazin-2-ylpyrrolo[3,2-d]
pyrimidine;
- 10 2-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)
benzo[b]furan;
- 2,7-Dimethyl-6-phenyl-4-piperidylpyrrolo[3,2-d]
pyrimidine;
- 6-Phenyl-4-piperidyl-2-(trifluoromethyl)pyrrolo[3,2-d]
pyrimidine;
- 15 6-(4-Chlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]
pyrimidine;
- (6-Phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-yl)
propylamine;
- 6-(tert-Butyl)-2-methyl-4-piperidylpyrrolo[3,2-d]
20 pyrimidine;
- 2-Methyl-6-(2-methylcyclopent-1-eneyl)-4-piperidyl
pyrrolo[3,2-d]pyrimidine;
- 2,5-Dimethyl-3-(2-methyl-4-piperidylpyrrolo[4,5-d]
pyrimidin-6-yl)thiophene;
- 25 2-Methyl-6-(4-phenylphenyl)-4-piperidylpyrrolo[3,2-d]
pyrimidine;
- 3-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)-1-
(phenylsulfonyl)pyrrole;
- 6-(2-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]
30 pyrimidine;
- 6-(3-Fluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-d]
pyrimidine;
- 2-Methyl-6-phenyl-4-(4-phenylpiperazinyl)pyrrolo[3,2-d]
pyrimidine;
- 35 2-Methyl-4-piperidyl-6-(3-(trifluoromethyl)phenyl)
pyrrolo[3,2-d]pyrimidine;
- 6-(2,6-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-
d]pyrimidine;
- 6-(2,5-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-
40 d]pyrimidine;
- 2-Methyl-4-piperidyl-6-(4-(trifluoromethyl)phenyl)
pyrrolo[3,2-d]pyrimidine;

- 2-Methyl-4-piperidyl-6-(2,3,4-trichlorophenyl)
pyrrolo[3,2-d]pyrimidine;
- 5-[2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-
2H-benzo[d]1,3-dioxolane;
- 5 2-Methyl-4-piperidyl-6-(3,4,5-trifluorophenyl)
pyrrolo[3,2-d]pyrimidine;
- 6-(3,5-Difluorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-
d]pyrimidine;
- 10 6-(3,4-Dichlorophenyl)-2-methyl-4-piperidylpyrrolo[3,2-
d]pyrimidine;
- 2-Fluoro-1-methoxy-4-[2-methyl-4-piperidylpyrrolo[4,5-
d]pyrimidin-6-yl]benzene;
- 2-Fluoro-4-[2-methyl-4-pyridylpyrrolo[4,5-d]pyrimidin-
6-yl]phenol;
- 15 6-((3,5-bis(Trifluoromethyl)phenyl)-2-methyl-4-
piperidylpyrrolo[3,2-d]pyrimidine;
- Trifluoro[4-(2-methyl-4-piperidylpyrrolo[4,5-d]
pyrimidin-6-yl)phenylthio]methane;
- 20 6-(3,4-Dimethylphenyl)-2-methyl-4-piperidylpyrrolo[3,2-
d]pyrimidine;
- 6-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)-
2H,3H-benzo[e]1,4-dioxane;
- 1,2-Dimethoxy-4-(2-methyl-4-piperidylpyrrolo[4,5-d]
pyrimidin-6-yl)benzene;
- 25 6-Fluoren-2-yl-2-methyl-4-piperidylpyrrolo[3,2-d]
pyrimidine;
- 2-Methyl-4-piperidyl-6-(2,5,6,7,8-tetrahydronaphthyl)
pyrrolo[3,2-d]pyrimidine;
- 30 2-Methyl-6-(5-methyl-1-phenylpyrazol-4-yl)-4-piperidyl
pyrrolo[3,2-d]pyrimidine;
- 6-Indan-5-yl-2-methyl-4-piperidylpyrrolo[3,2-d]
pyrimidine;
- 5-[2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl]-
2,3-dihydrobenzo[b]furan;
- 35 2,4-Dimethyl-5-[2-methyl-4-piperidylpyrrolo[4,5-d]
pyrimidin-6-yl]-1,3-thiazole;
- 2,7-Dimethyl-4-piperidyl-6-((4-trifluoromethyl)phenyl)
pyrrolo[3,2-d]pyrimidine;
- 40 6-(4-Fluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-
d]pyrimidine;
- 6-(3,4-Dichlorophenyl)-2,7-dimethyl-4-piperidyl
pyrrolo[3,2-d]pyrimidine;

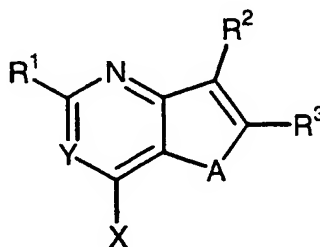
- 1-(2,7-Dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)-4-methoxybenzene;
4-(2,7-Dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenol;
5 6-(3,5-Difluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
1-(2,7-Dimethyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)-3-methoxybenzene;
4-(6-(3,4-Difluorophenyl)-2-methylpyrrolo[2,3-e]pyrimidin-4-yl)morpholine;
10 1-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)-4-(methylsulfonyl)benzene;
1,2,3-Trimethoxy-5-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzene;
15 7-Ethyl-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
5-(3-Chloro-4-fluorophenyl)-2-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)furan;
6-(4-Fluorophenyl)-2-methyl-4-(2-methylpiperidyl)pyrrolo[3,2-d]pyrimidine;
20 6-Butyl-2-methyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
2,6-Dimethyl-4-piperidyl-7-propylpyrrolo[3,2-d]pyrimidine;
1-(4-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenyl)ethan-1-one;
25 2-Methyl-6-(4-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenyl)-4-piperidylpyrrolo[3,2-d]pyrimidine;
7-Fluoro-2-methyl-6-piperidylpyrrolo[3,2-d]pyrimidine;
30 2-Methyl-6-phenyl-4-piperidyl-7-pyrrolidinylpyrrolo[3,2-d]pyrimidine;
3-Methyl-2-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzo[b]thiophene;
4-Chloro-1-((2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)methyl)sulfonyl)benzene;
35 4-Methoxy-1-((2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)methyl)benzene;
1-(2,6-Dimethyl-4-piperidylpyrrolo[3,2-d]pyrimidin-7-yl)-4-methoxybenzene;
40 2-Methyl-6-(2-naphthyl)-4-piperidylpyrrolo[3,2-d]pyrimidine;
3,5-Dimethyl-2-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)benzo[b]thiophene;

- 7-Methoxy-2-(2-methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)benzo[*b*]furan;
6-((4-Fluorophenyl)methyl)-2-methyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;
- 5 7-(4-Fluorophenyl)-2,6-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;
((2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)methoxy)benzene;
2,6-Dimethyl-7-phenoxy-4-piperidylpyrrolo[3,2-*d*]pyrimidine;
- 10 2-Methyl-6-(2-phenylethyl)-4-piperidylpyrrolo[3,2-*d*]pyrimidine;
2,6-Dimethyl-7-benzyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;
- 15 5-(2,7-Dimethyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)-2*H*-benzo[*d*]1,3-dioxolane;
6-(3,4-Difluorophenyl)-2,7-dimethyl-4-piperidylpyrrolo[3,2-*d*]pyrimidine;
- 20 1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl)piperidin-3-ol;
1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl)piperidin-4-ol;
8-Aza-8-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl)-1,4-dioxaspiro[4,5]decane;
- 25 1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl)-4-(3-(trifluoromethyl)phenyl)piperidin-4-ol;
1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidine-4-yl)piperidin-2-one;
- 30 2-Methyl-6-phenyl-4-piperidylpyrrolo[3,2-*d*]pyrimidin-1-ol;
4-((6*S*,2*R*)-2,6-Dimethyl)-2-methyl-6-phenylpyrrolo[3,2-*d*]pyrimidine;
4-((6*S*,2*R*)-2,6-Dimethylpiperidyl)-6-(4-fluorophenyl)-2-methylpyrrolo[3,2-*d*]pyrimidine;
- 35 3-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenylamine;
4-(2-Methyl-4-piperidylpyrrolo[4,5-*d*]pyrimidin-6-yl)phenylamine;
- 40 1-(2-Methyl-6-phenylpyrrolo[2,3-*e*]pyrimidin-4-yl)-4-naphthylsulfonyl)piperazine;
2-Methyl-6-phenyl-4-pyrrolidinylpyrrolo[3,2-*d*]pyrimidine;

- Trifluoro(4-(2-methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenoxy)methane;
6-Phenyl-4-piperidyl-2-propylpyrrolo[3,2-d]pyrimidine;
2-Methyl-4-(3-pyrrolinyl)-6-(3-(trifluoromethyl)phenyl)pyrrolo[3,2-d]pyrimidine;
5 6-(3-Chlorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo[3,2-d]pyrimidine;
6-(4-Fluorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo[3,2-d]pyrimidine;
10 6-Phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine-2-yl hydroxylamine;
6-(3,4-Dichlorophenyl)-2-methyl-4-(3-pyrrolinyl)pyrrolo[3,2-d]pyrimidine;
2-(2-Methylpropyl)-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
15 2-Ethyl-6-phenyl-4-(2-1,2,3,4-tetrahydroisoquinolyl)pyrrolo[3,2-d]pyrimidine;
2-Chloro-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
Dimethyl(6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidin-2-yl)amine;
20 2-Methoxy-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
Methyl(6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidin-2-yl)amine;
6-Phenyl-2-(4-phenylpiperazinyl)-4-piperidylpyrrolo[3,2-d]pyrimidine;
25 2-Cyclopropyl-6-(4-fluorophenyl)-4-piperidylpyrrolo[3,2-d]pyrimidine;
4-(2-Methyl-4-piperidylpyrrolo[4,5-d]pyrimidin-6-yl)phenyl 2,2-dimethylpropanoate;
30 7-Bromo-2-methyl-6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidine;
4-(8-azabicyclo[3.2.1]oct-8-yl)-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine;
(1-[2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-2-piperidyl)methan-1-ol;
35 4-Indolinyl-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine;
2-Methyl-6-phenyl-4-pyrazolypyrrolo[3,2-d]pyrimidine;
2-Methyl-6-phenyl-4-[1,2,4-triazolyl]pyrrolo[3,2-d]pyrimidine;
40 4-(2,5-Dimethyl(3-pyrrolinyl)-2-methyl-6-phenylpyrrolo[3,2-d]pyrimidine;

- 1-(2-Furanylcarbonyl)-4-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)piperazine;
 1-Acetyl-4-(2-methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)piperazine;
 5 1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)-4-(methylsulfonyl)piperazine;
 1-(2-Methyl-6-phenylpyrrolo[2,3-e]pyrimidin-4-yl)(phenylsulfonyl)piperazine;
 10 2-Methyl-5-phenyl-7,7a,8,9,10,11-hexahydro-1,3,11a-triaza-pyrrolo[3,2,1-de]phenanthridine;
 5-Methyl-2-(4-fluorophenyl)-7-piperidylpyrrolo[3,2-b]pyridine;
 (7-Aminoheptyl)-(6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidin-2-yl)amine; or
 15 (4-Aminobutyl)-(6-phenyl-4-piperidylpyrrolo[3,2-d]pyrimidin-2-yl)amine; or
 a pharmaceutically acceptable salt thereof.

- 20 10. A compound of formula



or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or C(R⁶); A is S, S(O), S(O)₂ or O;

- 25 R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, aryl, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl or -Z(Q) radical;
- 30 R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),

395

-Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
-Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical;

R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃,
5 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
-Z(aryloxy), -Z(aryl), -Z(heteroaryl),
-Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
-Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
-Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical,
10 provided that R² is not an optionally substituted
phenyl, pyridyl, pyrazinyl, pyrimidyl or pyridazinyl
radical;

R³ is a (C₃-C₁₀)cycloalkyl, (C₁-C₈)alkyl,
15 -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-,
-((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl),
-(CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mOH,
-(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH,
-(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)OH,
20 -(CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
-(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
-(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)(C₁-C₈)alkoxy,
-(CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mN(R⁵)₂,
-(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mN(R⁵)₂,
25 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)N(R⁵)₂,
-(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mS(O)_pR⁵, -D'(S(O)_qR⁵),
-D'(aryloxy), -D'(aryl), -D'(heteroaryl),
-D'((C₃-C₁₀)cycloalkyl), -D'(NR⁵SO₂R⁵), -D'(CON(R⁵)₂),
-D'(CO₂R⁵), -D'(NR⁵CON(R⁵)₂), -D'(NR⁵(CO)R⁵), -D'(NR⁵CO₂R⁵),
30 -D'(COR⁵), -D'(Q), -D(aryloxy), -D(aryl),
-D(heteroaryl), -D((C₃-C₁₀)cycloalkyl), -D(NR⁵SO₂R⁵),
-D(CON(R⁵)₂), -D(CO₂R⁵), -D(S(O)_qR⁵), -D(NR⁵CON(R⁵)₂),
-D(NR⁵(CO)R⁵), -D(NR⁵CO₂R⁵), -D(COR⁵) or -(NR⁵)_k-D-Q
radical;

35

- X is a (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl,
 -(NR⁵)_k((C₁-C₈)alkyl)(C₁-C₈)alkoxy,
 -(NR⁵)_k((C₁-C₈)alkyl)aryloxy, -(NR⁵)((C₁-C₈)alkyl)_kS(O)_pR⁵,
 -(NR⁵)_k((C₁-C₈)alkyl)S(O)_pR⁵, -(NR⁵)D(C₁-C₈)alkoxy,
 5 -(NR⁵)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
 -(NR⁵)_k(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
 -(NR⁵)_k(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
 -(NR⁵)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_maryloxy,
 -(NR⁵)_k(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_maryloxy,
 10 -(NR⁵)_k(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_maryloxy, -Z(S(O)_qR⁵),
 -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl),
 -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂),
 -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵) or
 -Z(Q) radical; or
 15 Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R⁵; wherein each R⁵ is independently a -OH,
 halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, -NH₂, -NH((C₁-C₈)alkyl),
 20 -N((C₁-C₈)alkyl)₂, or (C₁-C₈)alkyl radical;
 each R⁵ is independently a hydrogen, -OH, (C₁-C₈)alkoxy,
 aryl, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂,
 (C₁-C₈)alkyl or (C₃-C₁₀)cycloalkyl radical;
 25 D is -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m- and D' is
 -((C₁-C₈)alkyl)_k-;
 Z is D(NR⁵)_k, D'(NR⁵)_k, (NR⁵)_kD or (NR⁵)_kD';
 30 each k is independently 0 or 1;
 each m is independently an integer between 0 and 6;
 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and
 35

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R¹, R², R³, R⁵, R⁶ and R⁸ is optionally substituted with one or more radicals of halo, -CF₃, -OCF₃, -Z(COOH), -Z(OH),

5 -Z(NO₂), -Z(SH), -(C₁-C₈)alkyl, -(C₁-C₈)acyloxy, -(C₃-C₁₀)cycloalkyl, -S-((C₁-C₈)alkyl)_k-aryl, -((C₁-C₈)alkyl)_k-SO₂NH-aryl, -S-(C₁-C₈)alkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁹SO₂R⁹),

10 -Z(CON(R⁹)₂), -Z(CO₂R⁹), -Z(N(R⁹)₂), -Z(NR⁹CON(R⁹)₂), -Z(NR⁹(CO)R⁹), -Z(NR⁹CO₂R⁹), -Z(COR⁹), -Z(S(O)_pR⁹) or -Z(Q), wherein each R⁹ is independently a hydrogen or (C₁-C₈)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally

15 substituted with one or more radicals of halo, -NO₂, -CF₃, -OCF₃, -N(R⁹)₂, -C(O)R⁹, -CO₂R⁹, -OR⁹, -SR⁹ or (C₁-C₈)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹, R² and R³ is 0-4; and

20

provided that:

- (a) when A is S, Y is N, R² is H, R³ is methyl or phenyl and R¹ is phenyl, NH₂, piperazinyl or methyl, then X is not NH₂, morpholinyl, 1-oxidothiomorpholinyl or thiomorpholinyl;
- (b) when A is O, Y is C-H, R¹ is H, R² is H and R³ is propyl, butyl or hydroxypropyl, then X is not methyl, benzyl or methoxyphenyl-CH₂-;
- 30 (c) when A is S, Y is N, R² is H or alkyl, R³ is methyl, then R¹ is not nitro-furyl, -NH-(C₂-C₁₀)alkyl-NH₂, -N(alkyl)-(C₂-C₁₀)alkyl-NH₂ or -N(methyl)-ethyl-NHSO₂-tolyl;
- 35 (d) when A is S, Y is N, R² is H, halo, -NO₂ or alkyl, R³ is alkyl or phenyl and X is Q, -N(alkyl-OH)₂,

- N(methyl)-ethyl-S-methyl or -N(methyl)-ethyl-S(O)-methyl, then R^1 is not Q, -N(alkyl-OH)₂, -N(methyl)-ethyl-S-methyl or -N(methyl)-ethyl-S(O)-methyl;
- (e) when A is O or S, Y is CH, R^1 is H and R^2 is H, then
- 5 R^3 is not -SO₂NH₂;
- (f) when A is S, Y is N, R^1 is H and R^2 is H, then (1) when R^3 is phenyl, X is not -NH-NH₂, optionally substituted indolylalkylamino, optionally substituted indolylamino, optionally substituted
- 10 thiazolidinonylamino or optionally substituted azetidinonylamino, and (2) when R^3 is methyl, X is not piperidinyl; and
- (g) when A is O, Y is N, R^1 is optionally substituted phenyl, R^2 is H and R^3 is alkyl, then X is not
- 15 optionally substituted phenyl.

11. The compound of claim 10 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or C(R^6); A is S, S(O), S(O)₂ or O;
- 20

- R^6 is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, aryl, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂,
- 25 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl or -Z(Q) radical;

- R^1 is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
- 30 -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical, provided R^1 is not an optionally substituted aryl or heteroaryl radical;

R^2 is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
 -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
 -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
 5 -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵),
 -Z(S(O)_pR⁵) or -Z(Q) radical, provided that R² is not an
 optionally substituted aryl or heteroaryl radical;

R^3 is a (C₃-C₁₀)cycloalkyl, (C₃-C₈)alkyl,
 10 -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-,
 -((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl),
 -(CH₂)((C₃-C₁₀)cycloalkyl)_k(CH₂)_mOH,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)OH,
 15 -(CH₂)((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)(C₁-C₈)alkoxy,
 -(CH₂)((C₃-C₁₀)cycloalkyl)_k(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mN(R⁵)₂,
 20 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)N(R⁵)₂,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mS(O)_pR⁵,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(CO₂R⁵),
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(COR⁵),
 -((C₁-C₈)alkyl)(CO₂R⁵), -((C₁-C₈)alkyl)(COR⁵),
 25 -D'(S(O)_pR⁵), -D'(aryloxy), -D'(aryl), -D'(heteroaryl),
 -D'((C₃-C₁₀)cycloalkyl), -D'(NR⁵SO₂R⁵), -D'(CON(R⁵)₂),
 -D'(NR⁵CON(R⁵)₂), -D'(NR⁵(CO)R⁵), -D'(NR⁵CO₂R⁵), -D'(Q),
 -D(aryloxy), -D(aryl), -D(heteroaryl),
 -D((C₃-C₁₀)cycloalkyl), -D(NR⁵SO₂R⁵), -D(CON(R⁵)₂),
 30 -D(S(O)_pR⁵), -D(NR⁵CON(R⁵)₂), -D(NR⁵(CO)R⁵), -D(NR⁵CO₂R⁵) or
 -(NR⁵)_k-D-Q radical, provided R³ is not -SO₂NH₂;

X is a -(NR⁵)_k((C₁-C₈)alkyl)(C₁-C₈)alkoxy,
 -(NR⁵)_k((C₁-C₈)alkyl)aryloxy, -(NR⁵)((C₁-C₈)alkyl)_kS(O)_pR⁵,
 35 -(NR⁵)_k((C₁-C₈)alkyl)S(O)_pR⁵, -(NR⁵)D(C₁-C₈)alkoxy,
 -(NR⁵)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)(C₁-C₈)alkoxy,

- $-(NR^5)_k(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_m(C_1-C_8)\text{alkoxy},$
 $-(NR^5)_k(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_m(C_1-C_8)\text{alkoxy},$
 $-(NR^5)_k(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_m\text{aryloxy},$
 $-(NR^5)_k(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_m\text{aryloxy},$
5 $-(NR^5)_k(CH_2)_m((C_3-C_{10})\text{cycloalkyl})(CH_2)_m\text{aryloxy}, -Z(S(O)_2R^5),$
 $-Z(\text{aryl}), -Z(\text{heteroaryl}), -Z((C_3-C_{10})\text{cycloalkyl}),$
 $-Z(NR^5SO_2R^5), -Z(CON(R^5)_2), -Z(CO_2R^5), -Z(N(R^5)_2),$
 $-Z(NR^5CON(R^5)_2), -Z(NR^5(CO)R^5), -Z(NR^5CO_2R^5), -Z(COR^5) \text{ or}$
 $-Z(Q) \text{ radical; or}$
10 Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^6 ; wherein each R^6 is independently a $-OH$, halo, $-CF_3$, $-OCF_3$, $(C_1-C_8)\text{alkoxy}$, $-NH_2$, $-NH((C_1-C_8)\text{alkyl})$,
15 $-N((C_1-C_8)\text{alkyl})_2$, or $(C_1-C_8)\text{alkyl radical}$;
each R^5 is independently a hydrogen, $-OH$, $(C_1-C_8)\text{alkoxy}$, aryl, $-NH_2$, $-NH((C_1-C_8)\text{alkyl})$, $-N((C_1-C_8)\text{alkyl})_2$, $(C_1-C_8)\text{alkyl}$ or $(C_3-C_{10})\text{cycloalkyl radical}$;
20 D is $-(CH_2)_m((C_3-C_{10})\text{cycloalkyl})_k(CH_2)_m-$ and D' is $-((C_1-C_8)\text{alkyl})_k-$;
 Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;
25 each k is independently 0 or 1;
each m is independently an integer between 0 and 6;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and
30 wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q , alkoxy or aryloxy moiety of any of X , R^1 , R^2 , R^3 , R^5 and R^6 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$,
35 $-Z(NO_2)$, $-Z(SH)$, $-(C_1-C_8)\text{alkyl}$, $-(C_1-C_8)\text{acyloxy}$, $-(C_3-C_{10})\text{cycloalkyl}$, $-S-((C_1-C_8)\text{alkyl})_k\text{-aryl}$,

- ((C₁-C₈)alkyl)_x-SO₂NH-aryl, -S-(C₁-C₈)alkyl,
 -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl),
 -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁹SO₂R⁹),
 -Z(CON(R⁹)₂), -Z(CO₂R⁹), -Z(N(R⁹)₂), -Z(NR⁹CON(R⁹)₂),
 5 -Z(NR⁹(CO)R⁹), -Z(NR⁹CO₂R⁹), -Z(COR⁹), -Z(S(O)_pR⁹) or
 -Z(Q), wherein each R⁹ is independently a hydrogen or
 (C₁-C₈)alkyl radical and wherein such aryl, heteroaryl,
 cycloalkyl and Q substituents are optionally
 substituted with 1-3 radicals of halo, -NO₂, -CF₃,
 10 -OCF₃, -N(R⁹)₂, -C(O)R⁹, -CO₂R⁹, -OR⁹, -SR⁹ or (C₁-C₈)alkyl.

12. The compound of claim 11 or a
 pharmaceutically acceptable salt, ester, solvate or N-
 15 oxide thereof, wherein Y is N; A is S, S(O)₂ or O;

- R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₆)cycloalkyl, -Z((C₁-C₈)alkoxy),
 -Z((C₃-C₆)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(N(R⁵)₂) or -Z(Q)
 20 radical;

- R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
 -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
 25 -Z((C₃-C₁₀)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(CON(R⁵)₂),
 -Z(N(R⁵)₂), -Z(NR¹⁰CON(R⁵)₂), -Z(NR¹⁰(CO)R⁵), -Z(NR¹⁰CO₂R⁵),
 -Z(S(O)_pR⁵) or -Z(Q) radical, provided that R² is not an
 optionally substituted aryl or heteroaryl radical;

- 30 R³ is a (C₃-C₁₀)cycloalkyl, (C₃-C₈)alkyl,
 -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-,
 -((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl),
 -(CH₂)_x((C₃-C₁₀)cycloalkyl)_x(CH₂)_mOH,
 -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH,
 35 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_x(CH₂)_mOH,
 -(CH₂)_x((C₃-C₁₀)cycloalkyl)_x(CH₂)_m(C₁-C₈)alkoxy,

- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_m (C₁-C₈) alkoxy,
- (CH₂)_m ((C₃-C₁₀) cycloalkyl)_k (CH₂) (C₁-C₈) alkoxy,
- (CH₂) ((C₃-C₁₀) cycloalkyl)_k (CH₂)_m N(R⁵)₂,
- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_m N(R⁵)₂,
- 5 - (CH₂)_m ((C₃-C₁₀) cycloalkyl)_k (CH₂) N(R⁵)₂,
- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_m S(O)_p R⁵,
- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_m (CO₂ R⁵),
- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_m (COR⁵),
- ((C₁-C₈) alkyl) (CO₂ R⁵), - ((C₁-C₈) alkyl) (COR⁵),
- 10 -D' (S(O)_p R⁵), -D' (aryloxy), -D' (aryl), -D' (heteroaryl),
- D' ((C₃-C₁₀) cycloalkyl), -D' (NR¹⁰ SO₂ R⁵), -D' (CON(R⁵)₂),
- D' (NR¹⁰ CON(R⁵)₂), -D' (NR¹⁰ (CO) R⁵), -D' (NR¹⁰ CO₂ R⁵), -D' (Q),
- D(aryloxy), -D(aryl), -D(heteroaryl),
- D((C₃-C₁₀) cycloalkyl), -D(NR¹⁰ SO₂ R⁵), -D(CON(R⁵)₂),
- 15 -D(S(O)_p R⁵), -D(NR¹⁰ CON(R⁵)₂), -D(NR¹⁰ (CO) R⁵), -D(NR¹⁰ CO₂ R⁵)
- or - (NR¹⁰)_k-D-Q radical, provided R³ is not -SO₂NH₂;

- X is a - (NR¹⁰) ((C₁-C₈) alkyl) (C₁-C₈) alkoxy,
- (NR¹⁰) ((C₁-C₈) alkyl) aryloxy, - (NR¹⁰) S(O)_p R⁵,
 - 20 - (NR¹⁰) ((C₁-C₈) alkyl) S(O)_p R⁵, - (NR¹⁰) D(C₁-C₈) alkoxy,
 - (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl)_k (CH₂) (C₁-C₈) alkoxy,
 - (NR¹⁰) (CH₂) ((C₃-C₁₀) cycloalkyl)_k (CH₂)_m (C₁-C₈) alkoxy,
 - (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_m (C₁-C₈) alkoxy,
 - (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl)_k (CH₂) aryloxy,
 - 25 - (NR¹⁰) (CH₂) ((C₃-C₁₀) cycloalkyl)_k (CH₂)_m aryloxy,
 - (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_m aryloxy,
 - (NR¹⁰) D(S(O)_p R⁵), - (NR¹⁰) D' (S(O)_p R⁵), - (NR¹⁰) D(aryl),
 - (NR¹⁰) D' (aryl), - (NR¹⁰) D(heteroaryl),
 - (NR¹⁰) D' (heteroaryl), - (NR¹⁰) D((C₃-C₁₀) cycloalkyl),
 - 30 - (NR¹⁰) D' ((C₃-C₁₀) cycloalkyl), - (NR¹⁰) D(NR¹⁰ SO₂ R⁵),
 - (NR¹⁰) D' (NR¹⁰ SO₂ R⁵), - (NR¹⁰) D(CON(R⁵)₂), - (NR¹⁰) D' (CON(R⁵)₂),
 - (NR¹⁰) D(CO₂ R⁵), - (NR¹⁰) D' (CO₂ R⁵), - (NR¹⁰) D(N(R⁵)₂), - N(R⁵)₂,
 - (NR¹⁰) D' (N(R⁵)₂), - (NR¹⁰) D(NR¹⁰ CON(R⁵)₂),
 - (NR¹⁰) D' (NR¹⁰ CON(R⁵)₂), - (NR¹⁰) D(NR¹⁰ (CO) R⁵),
 - 35 - (NR¹⁰) D' (NR¹⁰ (CO) R⁵), - (NR¹⁰) D(NR¹⁰ CO₂ R⁵),

403

$-(NR^{10})D'(NR^{10}CO_2R^5)$, $-(NR^{10})D(COR^5)$, $-(NR^{10})D'(COR^5)$,
 $-(NR^{10})D-Q$, $-(NR^{10})D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or
 5 (C_1-C_4) alkyl radical; or

Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R^8 ; wherein each R^8 is independently a $-OH$,
 10 halo, $-CF_3$, $-OCF_3$, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$,
 $-N((C_1-C_4)alkyl)_2$, or $(C_1-C_4)alkyl$ radical;

each R^5 is independently a hydrogen, $-OH$, (C_1-C_4) alkoxy,
 $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, $(C_1-C_4)alkyl$ or
 15 (C_3-C_6) cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is
 $-((C_1-C_6)alkyl)_k-$;

20 Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
 each m is independently an integer between 0 and 4;
 each p is independently an integer between 0 and 2; and
 25 each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy
 moiety of any of X , R^1 , R^2 , R^3 and R^5 is optionally
 substituted with 1-3 radicals of halo and 1-2 radicals
 30 of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)alkyl$,
 $-(C_1-C_4)acyloxy$, $-(C_3-C_6)cycloalkyl$,
 $-S-((C_1-C_4)alkyl)_k-aryl$, $-((C_1-C_4)alkyl)_k-SO_2NH-aryl$,
 aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$,
 $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$,
 35 $-S(O)_2(C_1-C_4)alkyl$ or Q , wherein each R^9 is independently
 a hydrogen or $(C_1-C_4)alkyl$ radical and wherein such

aryl, heteroaryl, cycloalkyl and Q substituents are optionally substituted with 1-2 radicals of halo, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{N}(\text{R}^9)_2$, $-\text{C}(\text{O})\text{R}^9$, $-\text{CO}_2\text{R}^9$, $-\text{OR}^9$, $-\text{SR}^9$ or $(\text{C}_1\text{-C}_4)\text{alkyl}$; and

5

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1 , R^2 and R^3 is 0-3.

10

13. The compound of claim 12 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is S or O;

15 R^1 is a hydrogen, halo, $-\text{OH}$, $-\text{NO}_2$, $-\text{NHOH}$, $-\text{CF}_3$, $-\text{OCF}_3$, $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $-(\text{NR}^{10})_k((\text{C}_1\text{-C}_2)\text{alkyl})_k$ -cyclopropyl or $-(\text{NR}^{10})_k((\text{C}_1\text{-C}_2)\text{alkyl})_k\text{-N}(\text{R}^{10})_2$ radical;

R^2 is a hydrogen, chloro, fluoro, $-\text{CF}_3$, $-\text{OCF}_3$,
20 $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, $-(\text{NR}^{10})_k((\text{C}_1\text{-C}_2)\text{alkyl})_k$ - $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $-(\text{NR}^{10})_k((\text{C}_1\text{-C}_2)\text{alkyl})_k\text{-(CON}(\text{R}^5)_2)$,
 $-(\text{NR}^{10})_k((\text{C}_1\text{-C}_2)\text{alkyl})_k\text{-(N}(\text{R}^5)_2)$, $-(\text{NR}^{10})_k((\text{C}_1\text{-C}_2)\text{alkyl})_k$ - $(\text{S}(\text{O})_p\text{R}^5)$ or $-(\text{NR}^{10})_k((\text{C}_1\text{-C}_2)\text{alkyl})_k\text{-Q}$ radical;

25 R^3 is a $(\text{C}_3\text{-C}_6)\text{cycloalkyl}$, $(\text{C}_3\text{-C}_6)\text{alkyl}$,
 $-(\text{C}_1\text{-C}_4)\text{alkylOH}$, $(\text{C}_1\text{-C}_4)\text{alkoxy-(C}_1\text{-C}_4)\text{alkyl-}$,
 $-(\text{C}_1\text{-C}_4)\text{alkylN}(\text{R}^5)_2$, $-(\text{CH}_2)((\text{C}_3\text{-C}_6)\text{cycloalkyl})_k(\text{CH}_2)_m\text{OH}$,
 $-(\text{CH}_2)_m((\text{C}_3\text{-C}_6)\text{cycloalkyl})(\text{CH}_2)_m\text{OH}$,
 $-(\text{CH}_2)_m((\text{C}_3\text{-C}_6)\text{cycloalkyl})_k(\text{CH}_2)_m\text{OH}$,
30 $-(\text{CH}_2)((\text{C}_3\text{-C}_6)\text{cycloalkyl})_k(\text{CH}_2)_m(\text{C}_1\text{-C}_4)\text{alkoxy}$,
 $-(\text{CH}_2)_m((\text{C}_3\text{-C}_6)\text{cycloalkyl})(\text{CH}_2)_m(\text{C}_1\text{-C}_4)\text{alkoxy}$,
 $-(\text{CH}_2)_m((\text{C}_3\text{-C}_6)\text{cycloalkyl})_k(\text{CH}_2)_m(\text{C}_1\text{-C}_4)\text{alkoxy}$,
 $-(\text{CH}_2)((\text{C}_3\text{-C}_6)\text{cycloalkyl})_k(\text{CH}_2)_m\text{N}(\text{R}^5)_2$,
 $-(\text{CH}_2)_m((\text{C}_3\text{-C}_6)\text{cycloalkyl})(\text{CH}_2)_m\text{N}(\text{R}^5)_2$,
35 $-(\text{CH}_2)_m((\text{C}_3\text{-C}_6)\text{cycloalkyl})_k(\text{CH}_2)_m\text{N}(\text{R}^5)_2$,
 $-(\text{CH}_2)_m((\text{C}_3\text{-C}_6)\text{cycloalkyl})(\text{CH}_2)_m\text{S}(\text{O})_p\text{R}^5$,

$-(CH_2)_m((C_3-C_6) \text{ cycloalkyl})(CH_2)_m(CO_2R^5)$,
 $-(CH_2)_m((C_3-C_6) \text{ cycloalkyl})(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$,
 $-D'(\text{aryloxy})$, $-D'(\text{aryl})$, $-D'(\text{heteroaryl})$,
 $-D'((C_3-C_{10}) \text{ cycloalkyl})$, $-D'(Q)$, $-D(\text{aryloxy})$, $-D(\text{aryl})$,
 $-D(\text{heteroaryl})$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$,
 $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-$
 Q radical, provided R^3 is not $-SO_2NH_2$;

X is a $-(N((C_1-C_4)alkyl))-(C_1-C_4)aryloxy$,
10 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$,
15 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)aryloxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_maryloxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_maryloxy$,
 $-(N((C_1-C_4)alkyl))-D(aryl)$, $-(N((C_1-C_4)alkyl))-D'(aryl)$,
20 $-(N((C_1-C_4)alkyl))-D(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D'(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}SO_2R^5)$,
 $-(N((C_1-C_4)alkyl))-D(CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(N(R^5)_2)$, $-N(R^5)_2$,
 $-(N((C_1-C_4)alkyl))-D(NR^{10}CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}(CO)R^5)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CO_2R^5)$,
25 $-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))-D-Q$,
 $-(N((C_1-C_4)alkyl))-D'-Q$ or Q radical;

wherein each R¹⁰ is independently a hydrogen or
30 (C₁-C₄)alkyl radical; or

Q is a 4-membered to 10-membered heterocyclcyl or heteroaryl ring optionally substituted with 1-2 radicals of R⁸; wherein each R⁸ is independently a -OH, halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂, or (C₁-C₄)alkyl radical;

406

each R^5 is independently a hydrogen, -OH, (C_1-C_4) alkoxy, -NH₂, -NH $((C_1-C_4)$ alkyl), -N $((C_1-C_4)$ alkyl)₂ or (C_1-C_4) alkyl radical;

5

D is $-(CH_2)_m((C_3-C_6)$ cycloalkyl)_k(CH₂)_m- and D' is $-((C_1-C_4)$ alkyl)_k-;

Z is $(NR^{10})_xD$ or $(NR^{10})_xD'$;

10

each k is independently 0 or 1;
each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

15

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂, (C_1-C_4) alkyl, (C_1-C_4) acyloxy, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹,
20 -N(R⁹)₂, -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹ or
-S(O)₂(C₁-C₄)alkyl, wherein each R⁹ is independently a hydrogen or (C_1-C_4) alkyl radical; and

provided that the total number of aryl, heteroaryl,
25 cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1 , R^2 and R^3 is 1-3.

14. The compound of claim 13 or a
30 pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N; A is S or O;

R^1 is a bromo, chloro, fluoro, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C_1-C_2) alkyl, (C_1-C_2) alkoxy, $-(NR^{10})_x((C_1-C_2)$ alkyl)_x-
35 cyclopropyl, -NH₂ or -NH $((C_1-C_2)$ alkyl) radical;

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$,
 (C_1-C_2) alkyl or (C_1-C_2) alkoxy radical;

- 5 R^3 is a (C_3-C_6) cycloalkyl, (C_3-C_6) alkyl,
 $-((C_1-C_4)$ alkyl)OH, (C_1-C_4) alkoxy- (C_1-C_4) alkyl-,
 $-((C_1-C_4)$ alkyl) $N(R^5)_2$, $-(CH_2)((C_5-C_6)$ cycloalkyl) $_k(CH_2)_m$ OH,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_m$ OH,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $_k(CH_2)_m$ OH,
10 $-(CH_2)((C_5-C_6)$ cycloalkyl) $_k(CH_2)_m(C_1-C_2)$ alkoxy,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_m(C_1-C_2)$ alkoxy,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $_k(CH_2)_m(C_1-C_2)$ alkoxy,
 $-(CH_2)((C_5-C_6)$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_mN(R^5)_2$,
15 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_mS(O)_pR^5$,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_m(CO_2R^5)$,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$,
 $-D'(\text{aryloxy})$, $-D'(\text{aryl})$, $-D'(\text{heteroaryl})$,
20 $-D'((C_3-C_6)$ cycloalkyl), $-D'(Q)$, $-D(\text{aryloxy})$, $-D(\text{aryl})$,
 $-D(\text{heteroaryl})$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$,
 $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-$
 Q radical, provided R^3 is not $-SO_2NH_2$;

- 25 X is a $-N((C_1-C_4)$ alkyl) $_2$ or 4-membered to 10-membered
heterocyclyl or heteroaryl ring, having a nitrogen atom
ring member bonded directly to the carbon atom
adjoining X , optionally substituted with 1-2 radicals
of R^8 ;

30

wherein each R^{10} is independently a hydrogen or
 (C_1-C_2) alkyl radical; or

- 35 Q is a 4-membered to 10-membered heterocyclyl or
heteroaryl ring optionally substituted with 1-2
radicals of R^8 ; wherein each R^8 is independently a $-OH$,

halo, $-\text{CF}_3$, $-\text{OCF}_3$, $(\text{C}_1\text{-C}_2)\text{alkoxy}$, $-\text{NH}_2$, $-\text{NH}((\text{C}_1\text{-C}_2)\text{alkyl})$,
 $-\text{N}((\text{C}_1\text{-C}_2)\text{alkyl})_2$, or $(\text{C}_1\text{-C}_2)\text{alkyl radical}$;

each R^5 is independently a hydrogen, $-\text{OH}$, $(\text{C}_1\text{-C}_2)\text{alkoxy}$,
5 $-\text{NH}_2$, $-\text{NH}((\text{C}_1\text{-C}_2)\text{alkyl})$, $-\text{N}((\text{C}_1\text{-C}_2)\text{alkyl})_2$ or $(\text{C}_1\text{-C}_2)\text{alkyl radical}$;

D is $-(\text{CH}_2)_m((\text{C}_5\text{-C}_6)\text{cycloalkyl})_k(\text{CH}_2)_m-$ and D' is
 $-((\text{C}_1\text{-C}_4)\text{alkyl})_k-$;

10

Z is $(\text{NR}^{10})_k\text{D}$ or $(\text{NR}^{10})_k\text{D}'$;

each k is independently 0 or 1;

each m is independently an integer between 0 and 2;

15 each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy
moiety of any of X, R^2 and R^3 is optionally substituted
20 with 1-2 radicals of halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{NO}_2$,
 $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{acyloxy}$, $-\text{NR}^9\text{SO}_2\text{R}^9$, $-\text{CON}(\text{R}^9)_2$, $-\text{CO}_2\text{R}^9$,
 $-\text{N}(\text{R}^9)_2$, $-\text{NR}^9\text{CON}(\text{R}^9)_2$, $-\text{NR}^9(\text{CO})\text{R}^9$, $-\text{NR}^9\text{CO}_2\text{R}^9$, $-\text{COR}^9$ or
 $-\text{S}(\text{O})_2(\text{C}_1\text{-C}_4)\text{alkyl}$, wherein each R^9 is independently a
hydrogen or $(\text{C}_1\text{-C}_2)\text{alkyl radical}$; and

25

provided that the total number of aryl, heteroaryl,
cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1 ,
 R^2 and R^3 is 1-2.

30

15. The compound of claim 11 or a
pharmaceutically acceptable salt, ester, solvate or N-
oxide thereof, wherein Y is $\text{C}(\text{R}^6)$; A is S, $\text{S}(\text{O})_2$ or O;

R^6 is a hydrogen, -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, $(C_1-C_4)alkyl$ or $(C_3-C_6)cycloalkyl$ radical;

- 5 R^1 is a hydrogen, halo, -OH, $-NO_2$, $-NHOH$, $-CF_3$, $-OCF_3$, $(C_1-C_8)alkyl$, $(C_3-C_6)cycloalkyl$, $-Z((C_1-C_8)alkoxy)$, $-Z((C_3-C_6)cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(N(R^5)_2)$ or $-Z(Q)$ radical;
- 10 R^2 is a hydrogen, halo, -OH, $-NO_2$, $-CF_3$, $-OCF_3$, $(C_1-C_8)alkyl$, $(C_3-C_{10})cycloalkyl$, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^{10}SO_2R^5)$, $-Z(CON(R^5)_2)$, $-Z(N(R^5)_2)$, $-Z(NR^{10}CON(R^5)_2)$, $-Z(NR^{10}(CO)R^5)$, $-Z(NR^{10}CO_2R^5)$,
 15 $-Z(S(O)_pR^5)$ or $-Z(Q)$ radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

- R^3 is a $(C_3-C_{10})cycloalkyl$, $(C_3-C_8)alkyl$,
 $-((C_1-C_8)alkyl)OH$, $(C_1-C_8)alkoxy-(C_1-C_8)alkyl-$,
 20 $-((C_1-C_8)alkyl)N(R^5)_2$, $-((C_1-C_8)alkyl)S(O)_p((C_1-C_8)alkyl)$,
 $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mOH$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mOH$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)OH$,
 $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_m(C_1-C_8)alkoxy$,
 25 $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(C_1-C_8)alkoxy$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)(C_1-C_8)alkoxy$,
 $-(CH_2)((C_3-C_{10})cycloalkyl)_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$,
 30 $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_mS(O)_pR^5$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(CO_2R^5)$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_m(COR^5)$,
 $-((C_1-C_8)alkyl)(CO_2R^5)$, $-((C_1-C_8)alkyl)(COR^5)$,
 $-D'(S(O)_pR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$,
 35 $-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^{10}SO_2R^5)$, $-D'(CON(R^5)_2)$,
 $-D'(NR^{10}CON(R^5)_2)$, $-D'(NR^{10}(CO)R^5)$, $-D'(NR^{10}CO_2R^5)$, $-D'(Q)$,

-D(aryloxy), -D(aryl), -D(heteroaryl),
 -D((C₃-C₁₀) cycloalkyl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂),
 -D(S(O)_qR⁵), -D(NR¹⁰CON(R⁵)₂), -D(NR¹⁰(CO)R⁵), -D(NR¹⁰CO₂R⁵)
 or -(NR¹⁰)_k-D-Q radical, provided R³ is not -SO₂NH₂;

5

X is a -(NR¹⁰)((C₁-C₈)alkyl)(C₁-C₈)alkoxy,
 -(NR¹⁰)((C₁-C₈)alkyl)aryloxy, -(NR¹⁰)S(O)_pR⁵,
 -(NR¹⁰)((C₁-C₈)alkyl)S(O)_pR⁵, -(NR¹⁰)D(C₁-C₈)alkoxy,
 -(NR¹⁰)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
 10 -(NR¹⁰)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
 -(NR¹⁰)(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
 -(NR¹⁰)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_maryloxy,
 -(NR¹⁰)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_maryloxy,
 -(NR¹⁰)(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_maryloxy,
 15 -(NR¹⁰)D(S(O)_qR⁵), -(NR¹⁰)D'(S(O)_qR⁵), -(NR¹⁰)D(aryl),
 -(NR¹⁰)D'(aryl), -(NR¹⁰)D(heteroaryl),
 -(NR¹⁰)D'(heteroaryl), -(NR¹⁰)D((C₃-C₁₀)cycloalkyl),
 -(NR¹⁰)D'((C₃-C₁₀)cycloalkyl), -(NR¹⁰)D(NR¹⁰SO₂R⁵),
 -(NR¹⁰)D'(NR¹⁰SO₂R⁵), -(NR¹⁰)D(CON(R⁵)₂), -(NR¹⁰)D'(CON(R⁵)₂),
 20 -(NR¹⁰)D(CO₂R⁵), -(NR¹⁰)D'(CO₂R⁵), -(NR¹⁰)D(N(R⁵)₂), -N(R⁵)₂,
 -(NR¹⁰)D'(N(R⁵)₂), -(NR¹⁰)D(NR¹⁰CON(R⁵)₂),
 -(NR¹⁰)D'(NR¹⁰CON(R⁵)₂), -(NR¹⁰)D(NR¹⁰(CO)R⁵),
 -(NR¹⁰)D'(NR¹⁰(CO)R⁵), -(NR¹⁰)D(NR¹⁰CO₂R⁵),
 -(NR¹⁰)D'(NR¹⁰CO₂R⁵), -(NR¹⁰)D(COR⁵), -(NR¹⁰)D'(COR⁵),
 25 -(NR¹⁰)D-Q, -(NR¹⁰)D'-Q or Q radical;

wherein each R¹⁰ is independently a hydrogen or
 (C₁-C₄)alkyl radical; or

30 Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R⁸; wherein each R⁸ is independently a -OH,
 halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl),
 -N((C₁-C₄)alkyl)₂, or (C₁-C₄)alkyl radical;

35

each R^5 is independently a hydrogen, $-OH$, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, $(C_1-C_4)alkyl$ or $(C_3-C_6)cycloalkyl$ radical;

- 5 D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

- 10 each k is independently 0 or 1;
 each m is independently an integer between 0 and 4;
 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and
- 15 wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^5 and R^6 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)alkyl$, $-(C_1-C_4)acyloxy$, $-(C_3-C_6)cycloalkyl$,
- 20 $-S-((C_1-C_4)alkyl)_k-aryl$, $-((C_1-C_4)alkyl)_k-SO_2NH-aryl$, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$, $-S(O)_2(C_1-C_4)alkyl$ or Q, wherein each R^9 is independently a hydrogen or $(C_1-C_4)alkyl$ radical and wherein such
- 25 aryl, heteroaryl, cycloalkyl and Q substituents are optionally substituted with 1-2 radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or $(C_1-C_4)alkyl$; and
- 30 provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1 , R^2 and R^3 is 0-3.

16. The compound of claim 15 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is C(R⁶); A is S or O;

5 R⁶ is a hydrogen, -OH, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl), -N((C₁-C₂)alkyl)₂, or (C₁-C₄)alkyl radical;

10 R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-cyclopropyl or -(NR¹⁰)_k((C₁-C₂)alkyl)_k-N(R¹⁰)₂ radical;

15 R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(C₁-C₄)alkoxy, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(CON(R⁵)₂), -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(N(R⁵)₂), -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(S(O)_pR⁵) or -(NR¹⁰)_k((C₁-C₂)alkyl)_k-Q radical;

20 R³ is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl, -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-, -((C₁-C₄)alkyl)N(R⁵)₂, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₄)alkoxy, 25 -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₄)alkoxy, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₄)alkoxy, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂, 30 -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mS(O)_pR⁵, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_m(CO₂R⁵), -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_m(COR⁵), -D'(S(O)_qR⁵), -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'((C₃-C₁₀)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl), 35 -D(heteroaryl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂), -D(S(O)_qR⁵),

$-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-Q$ radical, provided R^3 is not $-SO_2NH_2$;

- X is a $-(N((C_1-C_4)alkyl))-(C_1-C_4)alkylaryloxy$,
- 5 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)(C_1-C_4)alkoxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_m(C_1-C_4)alkoxy$,
- 10 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)aryloxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)((C_3-C_6)cycloalkyl)_k(CH_2)_maryloxy$,
 $-(N((C_1-C_4)alkyl))-(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_maryloxy$,
 $-(N((C_1-C_4)alkyl))-D(aryl)$, $-(N((C_1-C_4)alkyl))-D'(aryl)$,
- 15 $-(N((C_1-C_4)alkyl))-D(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D'(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}SO_2R^5)$,
 $-(N((C_1-C_4)alkyl))-D(CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(N(R^5)_2)$, $-N(R^5)_2$,
 $-(N((C_1-C_4)alkyl))-D(NR^{10}CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}(CO)R^5)$,
- 20 $-(N((C_1-C_4)alkyl))-D(NR^{10}CO_2R^5)$,
 $-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))-D-Q$,
 $-(N((C_1-C_4)alkyl))-D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or
 25 $(C_1-C_4)alkyl$ radical; or

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8 ; wherein each R^8 is independently a -OH,
 30 halo, $-CF_3$, $-OCF_3$, $(C_1-C_4)alkoxy$, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or $(C_1-C_4)alkyl$ radical;

each R^5 is independently a hydrogen, -OH, $(C_1-C_4)alkoxy$, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$ or $(C_1-C_4)alkyl$
 35 radical;

D is $-(CH_2)_m((C_3-C_6)\text{cycloalkyl})_k(CH_2)_n-$ and D' is $-((C_1-C_4)\text{alkyl})_k-$;

5 Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;

each m is independently an integer between 0 and 3;

each p is independently an integer between 0 and 2; and

10 each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R² and R³ is optionally substituted with 1-2 radicals of halo, -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂,

15 (C₁-C₄)alkyl, (C₁-C₄)acyloxy, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹, -N(R⁹)₂, -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹ or -S(O)₂(C₁-C₄)alkyl, wherein each R⁹ is independently a hydrogen or (C₁-C₄)alkyl radical; and

20 provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹, R² and R³ is 1-3.

25 17. The compound of claim 16 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is C(R⁶); A is S or O;

R⁶ is a hydrogen, -OH, chloro, fluoro, -CF₃, -OCF₃,
30 (C₁-C₂)alkoxy or (C₁-C₂)alkyl radical;

R¹ is a bromo, chloro, fluoro, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₂)alkyl, (C₁-C₂)alkoxy, $-(NR^{10})_k((C_1-C_2)\text{alkyl})_k-$ cyclopropyl, -NH₂ or -NH((C₁-C₂)alkyl) radical;

35

R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2) alkyl or (C_1-C_2) alkoxy radical;

- R^3 is a (C_3-C_6) cycloalkyl, (C_3-C_6) alkyl,
- 5 $-((C_1-C_4)$ alkyl)OH, (C_1-C_4) alkoxy- (C_1-C_4) alkyl-,
 $-((C_1-C_4)$ alkyl) $N(R^5)_2$, $-(CH_2)((C_5-C_6)$ cycloalkyl) $_k(CH_2)_m$ OH,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_m$ OH,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $_k(CH_2)_m$ OH,
 $-(CH_2)((C_5-C_6)$ cycloalkyl) $_k(CH_2)_m(C_1-C_2)$ alkoxy,
 - 10 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_m(C_1-C_2)$ alkoxy,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $_k(CH_2)(C_1-C_2)$ alkoxy,
 $-(CH_2)((C_5-C_6)$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $_k(CH_2)N(R^5)_2$,
 - 15 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_mS(O)_pR^5$,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_m(CO_2R^5)$,
 $-(CH_2)_m((C_5-C_6)$ cycloalkyl) $(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$,
 $-D'(\text{aryloxy})$, $-D'(\text{aryl})$, $-D'(\text{heteroaryl})$,
 $-D'((C_3-C_6)$ cycloalkyl), $-D'(Q)$, $-D(\text{aryloxy})$, $-D(\text{aryl})$,
 - 20 $-D(\text{heteroaryl})$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$,
 $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-$
 Q radical, provided R^3 is not $-SO_2NH_2$;

X is a $-N((C_1-C_4)$ alkyl) $_2$ or 4-membered to 10-membered
 25 heterocyclyl or heteroaryl ring, having a nitrogen atom
 ring member bonded directly to the carbon atom
 adjoining X , optionally substituted with 1-2 radicals
 of R^8 ;

30 wherein each R^{10} is independently a hydrogen or
 (C_1-C_2) alkyl radical; or

Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 35 radicals of R^8 ; wherein each R^8 is independently a $-OH$,

halo, $-\text{CF}_3$, $-\text{OCF}_3$, $(\text{C}_1\text{-C}_2)\text{alkoxy}$, $-\text{NH}_2$, $-\text{NH}((\text{C}_1\text{-C}_2)\text{alkyl})$,
 $-\text{N}((\text{C}_1\text{-C}_2)\text{alkyl})_2$, or $(\text{C}_1\text{-C}_2)\text{alkyl radical}$;

each R^5 is independently a hydrogen, $-\text{OH}$, $(\text{C}_1\text{-C}_2)\text{alkoxy}$,
5 $-\text{NH}_2$, $-\text{NH}((\text{C}_1\text{-C}_2)\text{alkyl})$, $-\text{N}((\text{C}_1\text{-C}_2)\text{alkyl})_2$ or $(\text{C}_1\text{-C}_2)\text{alkyl radical}$;

D is $-(\text{CH}_2)_m((\text{C}_5\text{-C}_6)\text{cycloalkyl})_k(\text{CH}_2)_m-$ and D' is
 $-(\text{C}_1\text{-C}_4)\text{alkyl}_k-$;

10

Z is $(\text{NR}^{10})_k\text{D}$ or $(\text{NR}^{10})_k\text{D}'$;

each k is independently 0 or 1;

each m is independently an integer between 0 and 2;

15 each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy
moiety of any of X, R^2 and R^3 is optionally substituted
20 with 1-2 radicals of halo, $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{NO}_2$,
 $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{acyloxy}$, $-\text{NR}^9\text{SO}_2\text{R}^9$, $-\text{CON}(\text{R}^9)_2$, $-\text{CO}_2\text{R}^9$,
 $-\text{N}(\text{R}^9)_2$, $-\text{NR}^9\text{CON}(\text{R}^9)_2$, $-\text{NR}^9(\text{CO})\text{R}^9$, $-\text{NR}^9\text{CO}_2\text{R}^9$, $-\text{COR}^9$ or
 $-\text{S}(\text{O})_2(\text{C}_1\text{-C}_4)\text{alkyl}$, wherein each R^9 is independently a
hydrogen or $(\text{C}_1\text{-C}_2)\text{alkyl radical}$; and

25

provided that the total number of aryl, heteroaryl,
cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1 ,
 R^2 and R^3 is 1-2.

30

18. The compound of claim 10 which is:

2-Methyl-6-phenyl-4-piperidylthiopheno[3,2-d]
pyrimidine;

35 6-(4-Chlorophenyl)-2-methyl-4-piperidylthiopheno[3,2-d]
pyrimidine;

417

- 6-(*tert*-Butyl)-2-methyl-4-piperidylthiopheno[3,2-*d*]
pyrimidine;
6-(4-Chlorophenyl)-2-methyl-4-piperidinylfurano-[3,2-*d*]
pyrimidine;
5 6-(4-Chlorophenyl)-2-ethyl-4-piperidinylfurano[3,2-*d*]
pyrimidine;
6-(*tert*-Butyl)-2-methyl-4-piperidylthiopheno[3,2-*d*]
pyrimidin-1-ol;
2-Methyl-6-phenyl-4-piperidylthiopheno[3,2-*d*]pyrimidin-
10 1-ol;
6-(4-Chloro-phenyl)-2-methyl-4-piperidylthiopheno[3,2-*d*]
pyrimidin-1-ol;
6-Phenyl-4-piperidyl-2-(trifluoromethyl)thiophene[3,2-*d*]
pyrimidine;
15 2-Methyl-6-phenyl-4-(3-pyrrolinyl)furano[3,2-*d*]
pyrimidine;
6-(4-Fluorophenyl)-2-methyl-4-piperidylthiopheno[3,2-*d*]
pyrimidine;
2-Methyl-6-phenyl-4-(2-1,2,3,4-tetrahydroisoquinolyl)
20 thiopheno[3,2-*d*]pyrimidine;
2-Methyl-6-phenyl-4-(1,2,5,6-tetrahydropyridyl)
thiopheno[3,2-*d*]pyrimidine;
2-Methyl-6-phenyl-4-piperidylfurano[3,2-*d*]pyrimidine;
5-Methyl-2-phenyl-7-piperidylfurano[3,2-*b*]pyridine;
25 2-Butyl-5-methyl-7-piperidylfurano[3,2-*b*]pyridine;
2-(4-Fluorophenyl)-5-methyl-7-piperidylfurano[3,2-*b*]
pyridine; or
5-Methyl-7-piperidyl-2-(4-piperidylphenyl)furano[3,2-*b*]
pyridine; or
30 a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a
compound of claims 1 to 18 and a pharmaceutically
35 acceptable carrier.

20. Use of a compound of claims 1 to 18 for the
preparation of a composition for use in modulating
feeding behavior.

40

21. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of obesity.

5 22. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of diabetes.

10 23. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of a tumor disease.

15 24. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of an inflammatory disease or disorder.

20 25. Use of a compound of claims 1 to 18 for the preparation of a composition for use in the prophylaxis or treatment of a diseases or disorder which can be effected or facilitated by modulating CRF in a warm blooded animal.

25 26. Use of a compound of claims 1 to 18 for the preparation of a composition for use in treating
rheumatoid arthritis; osteoarthritis; pain; asthma;
psoriasis; allergies; generalized anxiety disorder;
panic; phobias; obsessive-compulsive disorder; post-
traumatic stress disorder; sleep disorders; stress-
induced psychotic episodes; pain perception;
30 fibromyalgia; mood disorders; depression; dysthemia;
bipolar disorders; cyclothymia; chronic fatigue
syndrome; stress-induced headache; cancer; irritable
bowel syndrome; Crohn's disease; spastic colon; post
operative ileus; ulcer; diarrhea; fever; human
35 immunodeficiency virus (HIV) infections;
neurodegenerative diseases; Alzheimer's disease;

Parkinson's disease; Huntington's disease;
gastrointestinal diseases; eating disorders; anorexia;
bulimia nervosa; hemorrhagic stress; chemical
dependencies; addictions; drug or alcohol withdrawal
5 symptoms; stress-induced psychotic episodes; euthyroid
sick syndrome; syndrome of inappropriate antidiarrhetic
hormone (ADH); obesity; infertility; head traumas;
spinal cord trauma; ischemic neuronal damage;
excitotoxic neuronal damage; epilepsy; stroke; immune
10 dysfunctions; muscular spasms; urinary incontinence;
senile dementia of the Alzheimer's type; multiinfarct
dementia; amyotrophic lateral sclerosis; hypertension;
tachycardia; congestive heart failure; osteoporosis;
premature birth; hypoglycemia; diarrhea; or colonic
15 hypersensitivity.

27. A method for modulating feeding behavior which
comprises administering to a warm blood animal an
effective amount of a compound of claims 1 to 18.

20

28. A method for the prophylaxis or treatment of
obesity which comprises administering to a warm blood
animal an effective amount of a compound of claims 1 to
18.

25

29. A method for the prophylaxis or treatment of
diabetes which comprises administering to a warm blood
animal an effective amount of a compound of claims 1 to
18.

30

30. A method for the prophylaxis or treatment of a
tumor disease in a warm blooded animal comprising
administering to the warm blooded animal an effective
amount of a compound of claims 1 to 18.

35

31. A method for the prophylaxis or treatment of an inflammatory disease or disorder comprising administering to the warm blood animal an effective amount of a compound of claims 1 to 18.

5

32. A method for the prophylaxis or treatment of a diseases or disorder which can be effected or facilitated by modulating CRF in a warm blooded animal comprising administering to the warm blood animal an effective amount of a compound of claims 1 to 18.

10

33. The method of Claim 32 wherein the disease or disorder is rheumatoid arthritis; osteoarthritis; pain; asthma; psoriasis; allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders; stress-induced psychotic episodes; pain perception; fibromyalgia; mood disorders; depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; fever; human immunodeficiency virus (HIV) infections; neurodegenerative diseases; Alzheimer's disease; Parkinson's disease; Huntington's disease; gastrointestinal diseases; eating disorders; anorexia; bulimia nervosa; hemorrhagic stress; chemical dependencies; addictions; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; hypertension;

15

20

25

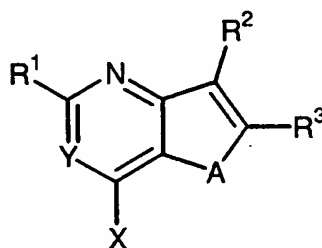
30

35

tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia; diarrhea; or colonic hypersensitivity.

5

34. A method for modulating feeding behavior, obesity or diabetes, or another disease state associated with the same or related pathway which modulates feeding behavior, obesity or diabetes which
 10 comprises administering to a warm blood animal an effective amount of a compound of formula



- or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof, wherein Y is N or C(R⁶); A is O, S,
 15 S(O), S(O)₂, N-H, N-R⁴ or CR⁴R⁷;

R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, -Z(aryl), -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl or -Z(Q) radical;

20

- R¹ and X are each independently a hydrogen, halo, -OH, -NO₂, -NHOH, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵),
 25 -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical; or

- X and A, when A is N or C, together with the adjoining
 30 carbon atoms form a 5-membered to 10-membered mono- or

bicyclic carbocyclic or heterocyclic ring which is optionally substituted with 1-2 radicals of R^8 ;

- R^2 and R^3 are each independently a hydrogen, halo, -OH,
 5 -NO₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
 -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
 -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
 -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
 -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q); provided R^2
 10 is not an optionally substituted aryl or heteroaryl radical;

- R^4 is a hydrogen, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl,
 -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl),
 15 -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵),
 -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂),
 -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q)
 radical;

- 20 each R^5 and R^7 are each independently a hydrogen, -OH,
 (C₁-C₈)alkoxy, aryl, -NH₂, -NH((C₁-C₈)alkyl),
 -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl or (C₃-C₁₀)cycloalkyl
 radical;

- 25 Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R^8 ; wherein each R^8 is independently a -OH,
 halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, -NH₂, -NH((C₁-C₈)alkyl),
 -N((C₁-C₈)alkyl)₂, or (C₁-C₈)alkyl radical;

- 30 Z is D(NR⁵)_k, D'(NR⁵)_k, (NR⁵)_kD or (NR⁵)_kD';

D is -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_n-; and D' is
 -((C₁-C₈)alkyl)_k-;

each k is independently 0 or 1;
 each m is independently an integer between 0 and 6;
 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and

5

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ is optionally substituted with one or more radicals of halo, -CF₃, -OCF₃, -Z(COOH), -Z(OH),
 10 -Z(NO₂), -Z(SH), -(C₁-C₈)alkyl, -(C₁-C₈)acyloxy, -(C₃-C₁₀)cycloalkyl, -S-((C₁-C₈)alkyl)_k-aryl, -((C₁-C₈)alkyl)_k-SO₂NH-aryl, -S-(C₁-C₈)alkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁹SO₂R⁹),
 15 -Z(CON(R⁹)₂), -Z(CO₂R⁹), -Z(N(R⁹)₂), -Z(NR⁹CON(R⁹)₂), -Z(NR⁹(CO)R⁹), -Z(NR⁹CO₂R⁹), -Z(COR⁹), -Z(S(O)_pR⁹) or -Z(Q), wherein each R⁹ is independently a hydrogen or (C₁-C₈)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substitutents are optionally
 20 substituted with one or more radicals of halo, -NO₂, -CF₃, -OCF₃, -N(R⁹)₂, -C(O)R⁹, -CO₂R⁹, -OR⁹, -SR⁹ or (C₁-C₈)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹, R² and R³ is 0-4.

35. The method of claim 34, wherein Y is N or
 30 C(R⁶); A is O, S, S(O), S(O)₂, N-H; N-R⁴ or CR⁴R⁷;

R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, aryl, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl or -Z(Q) radical;

35

R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
 -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
 -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
 5 -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
 -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical;

R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃,
 (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
 10 -Z(aryloxy), -Z(aryl), -Z(heteroaryl),
 -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
 -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
 -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical,
 provided that R² is not an optionally substituted aryl
 15 or heteroaryl radical;

R³ is a (C₃-C₁₀)cycloalkyl, (C₁-C₈)alkyl,
 -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-,
 -((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl),
 20 - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mOH,
 - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH,
 - (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)OH,
 - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
 - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
 25 - (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)(C₁-C₈)alkoxy,
 - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mN(R⁵)₂,
 - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mN(R⁵)₂,
 - (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)N(R⁵)₂,
 - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mS(O)_pR⁵, -D'(S(O)_qR⁵),
 30 -D'(aryloxy), -D'(aryl), -D'(heteroaryl),
 -D'((C₃-C₁₀)cycloalkyl), -D'(NR⁵SO₂R⁵), -D'(CON(R⁵)₂),
 -D'(CO₂R⁵), -D'(NR⁵CON(R⁵)₂), -D'(NR⁵(CO)R⁵), -D'(NR⁵CO₂R⁵),
 -D'(COR⁵), -D'(Q), -D(aryloxy), -D(aryl),
 -D(heteroaryl), -D((C₃-C₁₀)cycloalkyl), -D(NR⁵SO₂R⁵),
 35 -D(CON(R⁵)₂), -D(CO₂R⁵), -D(S(O)_qR⁵), -D(NR⁵CON(R⁵)₂),

-D(NR⁵(CO)R⁵), -D(NR⁵CO₂R⁵), -D(COR⁵) or -(NR⁵)_k-D-Q radical;

R⁴ is a (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl,

- 5 -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl),
 -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵),
 -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂),
 -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q)
 radical;

10

X is a (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl,

- (NR⁵)_k((C₁-C₈)alkyl)(C₁-C₈)alkoxy,
 - (NR⁵)_k((C₁-C₈)alkyl)aryloxy, - (NR⁵)((C₁-C₈)alkyl)_kS(O)_pR⁵,
 - (NR⁵)_k((C₁-C₈)alkyl)S(O)_pR⁵, - (NR⁵)D(C₁-C₈)alkoxy,
 15 - (NR⁵)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)(C₁-C₈)alkoxy,
 - (NR⁵)_k(CH₂)((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
 - (NR⁵)_k(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
 - (NR⁵)(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)aryloxy,
 - (NR⁵)_k(CH₂)((C₃-C₁₀)cycloalkyl)_k(CH₂)_maryloxy,
 20 - (NR⁵)_k(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_maryloxy, -Z(S(O)_pR⁵),
 -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl),
 -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂),
 -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(COR⁵) or
 -Z(Q) radical; or

25

X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic carbocyclic or heterocyclic ring which is optionally substituted with 1-2 radicals of R⁸;

30

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R⁸; wherein each R⁸ is independently a -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, -NH₂, -NH((C₁-C₈)alkyl),
 35 -N((C₁-C₈)alkyl)₂, or (C₁-C₈)alkyl radical;

each R^5 and R^7 are each independently a hydrogen, -OH, (C_1-C_8) alkoxy, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, $(C_1-C_8)alkyl$ or $(C_3-C_{10})cycloalkyl$
 5 radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

10 Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

each k is independently 0 or 1;
 each m is independently an integer between 0 and 6;
 each p is independently an integer between 0 and 2; and
 15 each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and R^8 is optionally substituted with one or more
 20 radicals of halo, $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$, $-Z(NO_2)$, $-Z(SH)$, $-(C_1-C_8)alkyl$, $-(C_1-C_8)acyloxy$, $-(C_3-C_{10})cycloalkyl$, $-S-((C_1-C_8)alkyl)_k-aryl$, $-((C_1-C_8)alkyl)_k-SO_2NH-aryl$, $-S-(C_1-C_8)alkyl$, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$,
 25 $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$, $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(O)_pR^9)$ or $-Z(Q)$, wherein each R^9 is independently a hydrogen or $(C_1-C_8)alkyl$ radical and wherein such aryl, heteroaryl,
 30 cycloalkyl and Q substituents are optionally substituted with one or more radicals of halo, $-NO_2$, $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or $(C_1-C_8)alkyl$;

35 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

36. The method of claim 35, wherein Y is N or C(R⁶); A is O, S, S(O), S(O)₂, N-H, N-R⁴ or CR⁴R⁷;

5

R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₈)alkoxy, aryl, -NH₂, -NH((C₁-C₈)alkyl), -N((C₁-C₈)alkyl)₂, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl or -Z(Q) radical;

- 10 R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
15 -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical;

R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl),

- 20 -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(S(O)_pR⁵) or -Z(Q) radical, provided that R² is not an optionally substituted aryl or heteroaryl radical;

- 25 R³ is a (C₃-C₁₀)cycloalkyl, (C₃-C₈)alkyl, -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-, -((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl), - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mOH, - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH,
30 - (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_kOH, - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy, - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy, - (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_k(C₁-C₈)alkoxy, - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mN(R⁵)₂,
35 - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mN(R⁵)₂, - (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_kN(R⁵)₂,

- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_n S(O)_p R⁵,
- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_n (CO₂ R⁵),
- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_n (COR⁵),
- ((C₁-C₈) alkyl) (CO₂ R⁵), - ((C₁-C₈) alkyl) (COR⁵),
- 5 -D' (S(O)_q R⁵), -D' (aryloxy), -D' (aryl), -D' (heteroaryl),
- D' ((C₃-C₁₀) cycloalkyl), -D' (NR⁵ SO₂ R⁵), -D' (CON(R⁵)₂),
- D' (NR⁵ CON(R⁵)₂), -D' (NR⁵ (CO) R⁵), -D' (NR⁵ CO₂ R⁵), -D' (Q),
- D(aryloxy), -D(aryl), -D(heteroaryl),
- D((C₃-C₁₀) cycloalkyl), -D(NR⁵ SO₂ R⁵), -D(CON(R⁵)₂),
- 10 -D(S(O)_q R⁵), -D(NR⁵ CON(R⁵)₂), -D(NR⁵ (CO) R⁵), -D(NR⁵ CO₂ R⁵) or
- (NR⁵)_x-D-Q radical;

- R⁴ is a (C₁-C₈) alkyl, (C₃-C₁₀) cycloalkyl,
- Z((C₁-C₈) alkoxy), -Z(aryloxy), -Z(aryl),
 - 15 -Z(heteroaryl), -Z((C₃-C₁₀) cycloalkyl), -Z(NR⁵ SO₂ R⁵),
 - Z(CON(R⁵)₂), -Z(CO₂ R⁵), -Z(N(R⁵)₂), -Z(NR⁵ CON(R⁵)₂),
 - Z(NR⁵ (CO) R⁵), -Z(NR⁵ CO₂ R⁵), -Z(COR⁵), -Z(S(O)_q R⁵) or -Z(Q)
- radical;

- 20 X is a -(NR⁵)_x((C₁-C₈) alkyl) (C₁-C₈) alkoxy,
- (NR⁵)_x((C₁-C₈) alkyl) aryloxy, -(NR⁵)((C₁-C₈) alkyl)_x S(O)_p R⁵,
 - (NR⁵)_x((C₁-C₈) alkyl) S(O)_p R⁵, -(NR⁵) D(C₁-C₈) alkoxy,
 - (NR⁵) (CH₂)_m ((C₃-C₁₀) cycloalkyl)_x (CH₂) (C₁-C₈) alkoxy,
 - (NR⁵)_x (CH₂) ((C₃-C₁₀) cycloalkyl)_x (CH₂)_m (C₁-C₈) alkoxy,
 - 25 -(NR⁵)_x (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_m (C₁-C₈) alkoxy,
 - (NR⁵) (CH₂)_m ((C₃-C₁₀) cycloalkyl)_x (CH₂) aryloxy,
 - (NR⁵)_x (CH₂) ((C₃-C₁₀) cycloalkyl)_x (CH₂)_m aryloxy,
 - (NR⁵)_x (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_m aryloxy, -Z(S(O)_q R⁵),
 - Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀) cycloalkyl),
 - 30 -Z(NR⁵ SO₂ R⁵), -Z(CON(R⁵)₂), -Z(CO₂ R⁵), -Z(N(R⁵)₂),
 - Z(NR⁵ CON(R⁵)₂), -Z(NR⁵ (CO) R⁵), -Z(NR⁵ CO₂ R⁵), -Z(COR⁵) or
 - Z(Q) radical; or

- X and A, when A is N or C, together with the adjoining
- 35 carbon atoms form a 5-membered to 10-membered mono- or

bicyclic carbocyclic or heterocyclic ring which is optionally substituted with 1-2 radicals of R^8 ;

- Q is a 4-membered to 10-membered heterocyclyl or
 5 heteroaryl ring optionally substituted with 1-2 radicals of R^8 ; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_8) alkoxy, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, or $(C_1-C_8)alkyl$ radical;
- 10 each R^5 and R^7 are each independently a hydrogen, -OH, $(C_1-C_8)alkoxy$, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$, $-N((C_1-C_8)alkyl)_2$, $(C_1-C_8)alkyl$ or $(C_3-C_{10})cycloalkyl$ radical;
- 15 D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_n-$ and D' is $-((C_1-C_8)alkyl)_k-$;
- Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;
- 20 each k is independently 0 or 1;
 each m is independently an integer between 0 and 6;
 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and
- 25 wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-Z(COOH)$, $-Z(OH)$, $-Z(NO_2)$, $-Z(SH)$, $-(C_1-C_8)alkyl$, $-(C_1-C_8)acyloxy$,
 30 $-(C_3-C_{10})cycloalkyl$, $-S-((C_1-C_8)alkyl)_k-aryl$, $-((C_1-C_8)alkyl)_k-SO_2NH-aryl$, $-S-(C_1-C_8)alkyl$, $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$, $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^9SO_2R^9)$, $-Z(CON(R^9)_2)$, $-Z(CO_2R^9)$, $-Z(N(R^9)_2)$, $-Z(NR^9CON(R^9)_2)$,
 35 $-Z(NR^9(CO)R^9)$, $-Z(NR^9CO_2R^9)$, $-Z(COR^9)$, $-Z(S(O)_pR^9)$ or $-Z(Q)$, wherein each R^9 is independently a hydrogen or

(C₁-C₈)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substituents are optionally substituted with 1-3 radicals of halo, -NO₂, -CF₃, -OCF₃, -N(R⁹)₂, -C(O)R⁹, -CO₂R⁹, -OR⁹, -SR⁹ or (C₁-C₈)alkyl;

5

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

10 37. The method of claim 36, wherein Y is N; A is O, S, S(O)₂, N-H, N-R⁴ or CHR⁴;

R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₆)cycloalkyl, -Z((C₁-C₈)alkoxy),
15 -Z((C₃-C₆)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(N(R⁵)₂) or -Z(Q) radical;

R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy),
20 -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(CON(R⁵)₂), -Z(N(R⁵)₂), -Z(NR¹⁰CON(R⁵)₂), -Z(NR¹⁰(CO)R⁵), -Z(NR¹⁰CO₂R⁵), -Z(S(O)_pR⁵) or -Z(Q) radical, provided that R² is not an optionally substituted aryl or heteroaryl radical;

25

R³ is a (C₃-C₁₀)cycloalkyl, (C₃-C₈)alkyl, -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-,
-((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl),
- (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_nOH,
30 - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH,
- (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_nOH,
- (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy,
- (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
- (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_k(C₁-C₈)alkoxy,
35 - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_nN(R⁵)₂,
- (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mN(R⁵)₂,

- (CH₂)_m ((C₃-C₁₀) cycloalkyl)_k (CH₂)N(R⁵)₂,
- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_n S(O)_p R⁵,
- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_n (CO₂R⁵),
- (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_n (COR⁵),
- 5 - ((C₁-C₈) alkyl) (CO₂R⁵), - ((C₁-C₈) alkyl) (COR⁵),
- D' (S(O)_q R⁵), - D' (aryloxy), - D' (aryl), - D' (heteroaryl),
- D' ((C₃-C₁₀) cycloalkyl), - D' (NR¹⁰ SO₂ R⁵), - D' (CON(R⁵)₂),
- D' (NR¹⁰ CON(R⁵)₂), - D' (NR¹⁰ (CO) R⁵), - D' (NR¹⁰ CO₂ R⁵), - D' (Q),
- D (aryloxy), - D (aryl), - D (heteroaryl),
- 10 - D ((C₃-C₁₀) cycloalkyl), - D (NR¹⁰ SO₂ R⁵), - D (CON(R⁵)₂),
- D (S(O)_q R⁵), - D (NR¹⁰ CON(R⁵)₂), - D (NR¹⁰ (CO) R⁵), - D (NR¹⁰ CO₂ R⁵)
- or - (NR¹⁰)_k-D-Q radical;

- R⁴ is a (C₁-C₄) alkyl, (C₃-C₆) cycloalkyl, -N(R⁵)₂ or -Z(Q)
- 15 radical;

- X is a - (NR¹⁰) ((C₁-C₈) alkyl) (C₁-C₈) alkoxy,
- (NR¹⁰) ((C₁-C₈) alkyl) aryloxy, - (NR¹⁰) S(O)_p R⁵,
 - (NR¹⁰) ((C₁-C₈) alkyl) S(O)_p R⁵, - (NR¹⁰) D (C₁-C₈) alkoxy,
 - 20 - (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl)_k (CH₂) (C₁-C₈) alkoxy,
 - (NR¹⁰) (CH₂) ((C₃-C₁₀) cycloalkyl)_k (CH₂)_n (C₁-C₈) alkoxy,
 - (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_n (C₁-C₈) alkoxy,
 - (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl)_k (CH₂) aryloxy,
 - (NR¹⁰) (CH₂) ((C₃-C₁₀) cycloalkyl)_k (CH₂)_n aryloxy,
 - 25 - (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_n aryloxy,
 - (NR¹⁰) D (S(O)_q R⁵), - (NR¹⁰) D' (S(O)_q R⁵), - (NR¹⁰) D (aryl),
 - (NR¹⁰) D' (aryl), - (NR¹⁰) D (heteroaryl),
 - (NR¹⁰) D' (heteroaryl), - (NR¹⁰) D ((C₃-C₁₀) cycloalkyl),
 - (NR¹⁰) D' ((C₃-C₁₀) cycloalkyl), - (NR¹⁰) D (NR¹⁰ SO₂ R⁵),
 - 30 - (NR¹⁰) D' (NR¹⁰ SO₂ R⁵), - (NR¹⁰) D (CON(R⁵)₂), - (NR¹⁰) D' (CON(R⁵)₂),
 - (NR¹⁰) D (CO₂ R⁵), - (NR¹⁰) D' (CO₂ R⁵), - (NR¹⁰) D (N(R⁵)₂), - N(R⁵)₂,
 - (NR¹⁰) D' (N(R⁵)₂), - (NR¹⁰) D (NR¹⁰ CON(R⁵)₂),
 - (NR¹⁰) D' (NR¹⁰ CON(R⁵)₂), - (NR¹⁰) D (NR¹⁰ (CO) R⁵),
 - (NR¹⁰) D' (NR¹⁰ (CO) R⁵), - (NR¹⁰) D (NR¹⁰ CO₂ R⁵),
 - 35 - (NR¹⁰) D' (NR¹⁰ CO₂ R⁵), - (NR¹⁰) D (COR⁵), - (NR¹⁰) D' (COR⁵),
 - (NR¹⁰) D-Q, - (NR¹⁰) D'-Q or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4) alkyl radical; or

- 5 X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclic ring which is optionally substituted with 1-2 radicals of R^8 ;
- 10 Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8 ; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or $(C_1-C_4)alkyl$ radical;
- 15 each R^5 is independently a hydrogen, -OH, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, $(C_1-C_4)alkyl$ or $(C_3-C_6)cycloalkyl$ radical;
- 20 D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;
 Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;
- 25 each k is independently 0 or 1;
 each m is independently an integer between 0 and 4;
 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and
- 30 wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^1 , R^2 , R^3 , R^4 and R^5 is optionally substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)alkyl$, $-(C_1-C_4)acyloxy$, $-(C_3-C_6)cycloalkyl$,
- 35 $-S-((C_1-C_4)alkyl)_k-aryl$, $-((C_1-C_4)alkyl)_k-SO_2NH-aryl$, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$,

-NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹,
 -S(O)₂(C₁-C₄)alkyl or Q, wherein each R⁹ is independently
 a hydrogen or (C₁-C₄)alkyl radical and wherein such
 aryl, heteroaryl, cycloalkyl and Q substituents are
 5 optionally substituted with 1-2 radicals of halo, -NO₂,
 -CF₃, -OCF₃, -N(R⁹)₂, -C(O)R⁹, -CO₂R⁹, -OR⁹, -SR⁹ or
 (C₁-C₄)alkyl; and

provided that the total number of aryl, heteroaryl,
 10 cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹,
 R² and R³ is 0-3;

or a pharmaceutically acceptable salt, ester, solvate
 or N-oxide thereof.

15

38. The method of claim 37, wherein Y is N; A is
 O, S, N-H or N-R⁴;

20 R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃,
 (C₁-C₄)alkyl, (C₁-C₄)alkoxy, -(NR¹⁰)_x((C₁-C₂)alkyl)_x-
 cyclopropyl or -(NR¹⁰)_x((C₁-C₂)alkyl)_x-N(R¹⁰)₂ radical;

R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃,
 25 (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, -(NR¹⁰)_x((C₁-C₂)alkyl)_x-
 (C₁-C₄)alkoxy, -(NR¹⁰)_x((C₁-C₂)alkyl)_x-(CON(R⁵)₂),
 -(NR¹⁰)_x((C₁-C₂)alkyl)_x-(N(R⁵)₂), -(NR¹⁰)_x((C₁-C₂)alkyl)_x-
 (S(O)_pR⁵) or -(NR¹⁰)_x((C₁-C₂)alkyl)_x-Q radical;

30 R³ is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl,
 -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-,
 -((C₁-C₄)alkyl)N(R⁵)₂, -(CH₂)_x((C₃-C₆)cycloalkyl)_x(CH₂)_mOH,
 -(CH₂)_m((C₃-C₆)cycloalkyl)(CH₂)_mOH,
 -(CH₂)_m((C₃-C₆)cycloalkyl)_x(CH₂)OH,
 35 -(CH₂)_x((C₃-C₆)cycloalkyl)_x(CH₂)_m(C₁-C₄)alkoxy,
 -(CH₂)_m((C₃-C₆)cycloalkyl)(CH₂)_m(C₁-C₄)alkoxy,

- (CH₂)_m ((C₃-C₆) cycloalkyl)_k (CH₂) (C₁-C₄) alkoxy,
 - (CH₂) ((C₃-C₆) cycloalkyl)_k (CH₂)_m N(R⁵)₂,
 - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m N(R⁵)₂,
 - (CH₂)_m ((C₃-C₆) cycloalkyl)_k (CH₂) N(R⁵)₂,
 - 5 - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m S(O)_p R⁵,
 - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m (CO₂ R⁵),
 - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m (COR⁵), -D' (S(O)_q R⁵),
 - D' (aryloxy), -D' (aryl), -D' (heteroaryl),
 - D' ((C₃-C₁₀) cycloalkyl), -D' (Q), -D (aryloxy), -D (aryl),
 - 10 -D (heteroaryl), -D (NR¹⁰ SO₂ R⁵), -D (CON(R⁵)₂), -D (S(O)_q R⁵),
 - D (NR¹⁰ CON(R⁵)₂), -D (NR¹⁰ (CO) R⁵), -D (NR¹⁰ CO₂ R⁵) or - (NR¹⁰)_k -D-
- Q radical;

R⁴ is a (C₁-C₄) alkyl radical;

- 15
- X is a - (N((C₁-C₄) alkyl)) - ((C₁-C₄) alkyl) aryloxy,
- (N((C₁-C₄) alkyl)) -
- (CH₂)_m ((C₃-C₆) cycloalkyl)_k (CH₂) (C₁-C₄) alkoxy,
- (N((C₁-C₄) alkyl)) -
- 20 (CH₂) ((C₃-C₆) cycloalkyl)_k (CH₂)_m (C₁-C₄) alkoxy,
- (N((C₁-C₄) alkyl)) -
- (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m (C₁-C₄) alkoxy,
- (N((C₁-C₄) alkyl)) - (CH₂)_m ((C₃-C₆) cycloalkyl)_k (CH₂) aryloxy,
- (N((C₁-C₄) alkyl)) - (CH₂) ((C₃-C₆) cycloalkyl)_k (CH₂)_m aryloxy,
- 25 - (N((C₁-C₄) alkyl)) - (CH₂)_m ((C₃-C₆) cycloalkyl) (CH₂)_m aryloxy,
- (N((C₁-C₄) alkyl)) - D (aryl), - (N((C₁-C₄) alkyl)) - D' (aryl),
- (N((C₁-C₄) alkyl)) - D (heteroaryl), - (N((C₁-C₄) alkyl)) -
- D' (heteroaryl), - (N((C₁-C₄) alkyl)) - D (NR¹⁰ SO₂ R⁵),
- (N((C₁-C₄) alkyl)) - D (CON(R⁵)₂), - (N((C₁-C₄) alkyl)) -
- 30 D (CO₂ R⁵), - (N((C₁-C₄) alkyl)) - D (N(R⁵)₂), - N(R⁵)₂,
- (N((C₁-C₄) alkyl)) - D (NR¹⁰ CON(R⁵)₂), - (N((C₁-C₄) alkyl)) -
- D (NR¹⁰ (CO) R⁵), - (N((C₁-C₄) alkyl)) - D (NR¹⁰ CO₂ R⁵),
- (N((C₁-C₄) alkyl)) - D (COR⁵), - (N((C₁-C₄) alkyl)) - D-Q,
- (N((C₁-C₄) alkyl)) - D'-Q or Q radical;

wherein each R^{10} is independently a hydrogen or (C_1-C_4) alkyl radical; or

5 X and A, when A is N, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8 ;

10 Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8 ; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or $(C_1-C_4)alkyl$ radical;

15 each R^5 is independently a hydrogen, -OH, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$ or $(C_1-C_4)alkyl$ radical;

20 D is $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;
25 each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

30 wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 and R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $(C_1-C_4)alkyl$, $(C_1-C_4)acyloxy$, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(O)_2(C_1-C_4)alkyl$, wherein each R^9 is independently a
35 hydrogen or $(C_1-C_4)alkyl$ radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹, R² and R³ is 1-3;

5

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

10 39. The method of claim 38, wherein Y is N; A is O, S or N-H;

R¹ is a bromo, chloro, fluoro, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₂)alkyl, (C₁-C₂)alkoxy, -(NR¹⁰)_x((C₁-C₂)alkyl)_x-
15 cyclopropyl, -NH₂ or -NH((C₁-C₂)alkyl) radical;

R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₂)alkyl or (C₁-C₂)alkoxy radical;

20 R³ is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl, -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-, -((C₁-C₄)alkyl)N(R⁵)₂, -(CH₂)_k((C₅-C₆)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mOH, -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)OH,
25 -(CH₂)_k((C₅-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₂)alkoxy, -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(C₁-C₂)alkoxy, -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)(C₁-C₂)alkoxy, -(CH₂)_k((C₅-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂, -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mN(R⁵)₂,
30 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)N(R⁵)₂, -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mS(O)_pR⁵, -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(CO₂R⁵), -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(COR⁵), -D'(S(O)_qR⁵), -D'(aryloxy), -D'(aryl), -D'(heteroaryl),
35 -D'((C₃-C₆)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂), -D(S(O)_qR⁵),

$-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-Q$ radical;

5 X is a $-N((C_1-C_4)alkyl)_2$ or 4-membered to 10-membered heterocyclyl or heteroaryl ring, having a nitrogen atom ring member bonded directly to the carbon atom adjoining X, optionally substituted with 1-2 radicals of R^8 ;

10 wherein each R^{10} is independently a hydrogen or $(C_1-C_2)alkyl$ radical; or

15 X and A, when A is N, together with the adjoining carbon atoms form a 8-membered to 10-membered bicyclic heterocyclyl moiety which is optionally substituted with 1-2 radicals of R^8 ;

20 Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R^8 ; wherein each R^8 is independently a $-OH$, halo, $-CF_3$, $-OCF_3$, $(C_1-C_2)alkoxy$, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$, or $(C_1-C_2)alkyl$ radical;

25 each R^5 is independently a hydrogen, $-OH$, $(C_1-C_2)alkoxy$, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or $(C_1-C_2)alkyl$ radical;

30 D is $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;

each m is independently an integer between 0 and 2;

35 each p is independently an integer between 0 and 2; and

each q is independently 1 or 2; and

- wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R² and R³ is optionally substituted
- 5 with 1-2 radicals of halo, -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂, (C₁-C₄)alkyl, (C₁-C₄)acyloxy, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹, -N(R⁹)₂, -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹ or -S(O)₂(C₁-C₄)alkyl, wherein each R⁹ is independently a hydrogen or (C₁-C₂)alkyl radical; and
- 10 provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹, R² and R³ is 1-2;
- 15 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

40. The method of claim 36, wherein Y is C(R⁶); A
- 20 is O, S, S(O)₂, N-H, N-R⁴ or CHR⁴;

R⁶ is a hydrogen, -OH, halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl radical;

- 25 R¹ is a hydrogen, halo, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₆)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z((C₃-C₆)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(N(R⁵)₂) or -Z(Q) radical;

- 30 R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(CON(R⁵)₂),
- 35 -Z(N(R⁵)₂), -Z(NR¹⁰CON(R⁵)₂), -Z(NR¹⁰(CO)R⁵), -Z(NR¹⁰CO₂R⁵),

$-Z(S(O)_pR^5)$ or $-Z(Q)$ radical, provided that R^2 is not an optionally substituted aryl or heteroaryl radical;

R^3 is a (C_3-C_{10}) cycloalkyl, (C_3-C_8) alkyl,

- 5 $-((C_1-C_8)$ alkyl)OH, (C_1-C_8) alkoxy- (C_1-C_8) alkyl-,
 $-((C_1-C_8)$ alkyl) $N(R^5)_2$, $-((C_1-C_8)$ alkyl) $S(O)_p((C_1-C_8)$ alkyl),
 $-(CH_2)((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m$ OH,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m$ OH,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)$ OH,
- 10 $-(CH_2)((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)(C_1-C_8)$ alkoxy,
 $-(CH_2)((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_mN(R^5)_2$,
- 15 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)N(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_mS(O)_pR^5$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(CO_2R^5)$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(COR^5)$,
 $-((C_1-C_8)$ alkyl) (CO_2R^5) , $-((C_1-C_8)$ alkyl) (COR^5) ,
- 20 $-D'(S(O)_pR^5)$, $-D'(\text{aryloxy})$, $-D'(\text{aryl})$, $-D'(\text{heteroaryl})$,
 $-D'((C_3-C_{10})$ cycloalkyl), $-D'(NR^{10}SO_2R^5)$, $-D'(CON(R^5)_2)$,
 $-D'(NR^{10}CON(R^5)_2)$, $-D'(NR^{10}(CO)R^5)$, $-D'(NR^{10}CO_2R^5)$, $-D'(Q)$,
 $-D(\text{aryloxy})$, $-D(\text{aryl})$, $-D(\text{heteroaryl})$,
 $-D((C_3-C_{10})$ cycloalkyl), $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$,
- 25 $-D(S(O)_pR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$
or $-(NR^{10})_k-D-Q$ radical;

R^4 is a (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, $-N(R^5)_2$ or $-Z(Q)$ radical;

30

- X is a $-(NR^{10})((C_1-C_8)$ alkyl) (C_1-C_8) alkoxy,
 $-(NR^{10})((C_1-C_8)$ alkyl)aryloxy, $-(NR^{10})S(O)_pR^5$,
 $-(NR^{10})((C_1-C_8)$ alkyl) $S(O)_pR^5$, $-(NR^{10})D(C_1-C_8)$ alkoxy,
 $-(NR^{10})(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)(C_1-C_8)$ alkoxy,
35 $-(NR^{10})(CH_2)((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(NR^{10})(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(C_1-C_8)$ alkoxy,

- (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl)_k (CH₂)_n aryloxy,
- (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl)_k (CH₂)_n aryloxy,
- (NR¹⁰) (CH₂)_m ((C₃-C₁₀) cycloalkyl) (CH₂)_n aryloxy,
- (NR¹⁰) D(S(O)_qR⁵), - (NR¹⁰) D'(S(O)_qR⁵), - (NR¹⁰) D(aryl),
- 5 - (NR¹⁰) D'(aryl), - (NR¹⁰) D(heteroaryl),
- (NR¹⁰) D'(heteroaryl), - (NR¹⁰) D((C₃-C₁₀) cycloalkyl),
- (NR¹⁰) D'((C₃-C₁₀) cycloalkyl), - (NR¹⁰) D(NR¹⁰SO₂R⁵),
- (NR¹⁰) D'(NR¹⁰SO₂R⁵), - (NR¹⁰) D(CON(R⁵)₂), - (NR¹⁰) D'(CON(R⁵)₂),
- (NR¹⁰) D(CO₂R⁵), - (NR¹⁰) D'(CO₂R⁵), - (NR¹⁰) D(N(R⁵)₂), - N(R⁵)₂,
- 10 - (NR¹⁰) D'(N(R⁵)₂), - (NR¹⁰) D(NR¹⁰CON(R⁵)₂),
- (NR¹⁰) D'(NR¹⁰CON(R⁵)₂), - (NR¹⁰) D(NR¹⁰(CO)R⁵),
- (NR¹⁰) D'(NR¹⁰(CO)R⁵), - (NR¹⁰) D(NR¹⁰CO₂R⁵),
- (NR¹⁰) D'(NR¹⁰CO₂R⁵), - (NR¹⁰) D(COR⁵), - (NR¹⁰) D'(COR⁵),
- (NR¹⁰) D-Q, - (NR¹⁰) D'-Q or Q radical;

15

wherein each R¹⁰ is independently a hydrogen or (C₁-C₄)alkyl radical; or

- 20 X and A, when A is N or C, together with the adjoining carbon atoms form a 5-membered to 10-membered mono- or bicyclic heterocyclic ring which is optionally substituted with 1-2 radicals of R⁸;

- 25 Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R⁸; wherein each R⁸ is independently a -OH, halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂, or (C₁-C₄)alkyl radical;

- 30 each R⁵ is independently a hydrogen, -OH, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂, (C₁-C₄)alkyl or (C₃-C₆)cycloalkyl radical;

- 35 D is -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_n- and D' is -((C₁-C₈)alkyl)_k-;

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;

- 5 each m is independently an integer between 0 and 4;
 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and

- wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy
 10 moiety of any of X, R^1 , R^2 , R^3 , R^4 , R^5 and R^6 is
 optionally substituted with 1-3 radicals of halo and 1-
 2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$,
 $-(C_1-C_4)alkyl$, $-(C_1-C_4)acyloxy$, $-(C_3-C_6)cycloalkyl$,
 $-S-((C_1-C_4)alkyl)_k-aryl$, $-((C_1-C_4)alkyl)_k-SO_2NH-aryl$,
 15 aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$,
 $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$,
 $-S(O)_2(C_1-C_4)alkyl$ or Q, wherein each R^9 is independently
 a hydrogen or $(C_1-C_4)alkyl$ radical and wherein such
 aryl, heteroaryl, cycloalkyl and Q substituents are
 20 optionally substituted with 1-2 radicals of halo, $-NO_2$,
 $-CF_3$, $-OCF_3$, $-N(R^9)_2$, $-C(O)R^9$, $-CO_2R^9$, $-OR^9$, $-SR^9$ or
 $(C_1-C_4)alkyl$; and

- provided that the total number of aryl, heteroaryl,
 25 cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1 ,
 R^2 and R^3 is 0-3;

or a pharmaceutically acceptable salt, ester, solvate
 or N-oxide thereof.

30

41. The method of claim 40, wherein Y is $C(R^6)$; A
 is O, S, N-H or $N-R^4$;

R^6 is a hydrogen, -OH, chloro, fluoro, $-CF_3$, $-OCF_3$, (C_1-C_2) alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or $(C_1-C_4)alkyl$ radical;

- 5 R^1 is a hydrogen, halo, -OH, $-NO_2$, $-NHOH$, $-CF_3$, $-OCF_3$, $(C_1-C_4)alkyl$, $(C_1-C_4)alkoxy$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-$ cyclopropyl or $-(NR^{10})_k((C_1-C_2)alkyl)_k-N(R^{10})_2$ radical;

- R^2 is a hydrogen, chloro, fluoro, $-CF_3$, $-OCF_3$,
 10 $(C_1-C_4)alkyl$, $(C_3-C_6)cycloalkyl$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-$ $(C_1-C_4)alkoxy$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(CON(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(N(R^5)_2)$, $-(NR^{10})_k((C_1-C_2)alkyl)_k-(S(O)_pR^5)$ or $-(NR^{10})_k((C_1-C_2)alkyl)_k-Q$ radical;

- 15 R^3 is a $(C_3-C_6)cycloalkyl$, $(C_3-C_6)alkyl$, $-((C_1-C_4)alkyl)OH$, $(C_1-C_4)alkoxy-(C_1-C_4)alkyl-$, $-((C_1-C_4)alkyl)N(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_mOH$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_mOH$,
 20 $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m(C_1-C_4)alkoxy$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$,
 25 $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_mN(R^5)_2$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_mS(O)_pR^5$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m(CO_2R^5)$, $-(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_m(COR^5)$, $-D'(S(O)_qR^5)$, $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$,
 30 $-D'((C_3-C_{10})cycloalkyl)$, $-D'(Q)$, $-D(aryloxy)$, $-D(aryl)$, $-D(heteroaryl)$, $-D(NR^{10}SO_2R^5)$, $-D(CON(R^5)_2)$, $-D(S(O)_qR^5)$, $-D(NR^{10}CON(R^5)_2)$, $-D(NR^{10}(CO)R^5)$, $-D(NR^{10}CO_2R^5)$ or $-(NR^{10})_k-D-Q$ radical;

- 35 R^4 is a $(C_1-C_4)alkyl$ radical;

- X is a $-(N((C_1-C_4)alkyl))-((C_1-C_4)alkyl)aryloxy$,
 $-(N((C_1-C_4)alkyl))-$
 $(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_n(C_1-C_4)alkoxy$,
5 $-(N((C_1-C_4)alkyl))-$
 $(CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_n(C_1-C_4)alkoxy$,
 $-(N((C_1-C_4)alkyl))-$
 $(CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_n(C_1-C_4)alkoxy$,
 $-(N((C_1-C_4)alkyl))- (CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_naryloxy$,
10 $-(N((C_1-C_4)alkyl))- (CH_2)_m((C_3-C_6)cycloalkyl)_k(CH_2)_naryloxy$,
 $-(N((C_1-C_4)alkyl))- (CH_2)_m((C_3-C_6)cycloalkyl)(CH_2)_naryloxy$,
 $-(N((C_1-C_4)alkyl))-D(aryl)$, $-(N((C_1-C_4)alkyl))-D'(aryl)$,
 $-(N((C_1-C_4)alkyl))-D(heteroaryl)$, $-(N((C_1-C_4)alkyl))-$
 $D'(heteroaryl)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}SO_2R^5)$,
15 $-(N((C_1-C_4)alkyl))-D(CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-$
 $D(CO_2R^5)$, $-(N((C_1-C_4)alkyl))-D(N(R^5)_2)$, $-N(R^5)_2$,
 $-(N((C_1-C_4)alkyl))-D(NR^{10}CON(R^5)_2)$, $-(N((C_1-C_4)alkyl))-$
 $D(NR^{10}(CO)R^5)$, $-(N((C_1-C_4)alkyl))-D(NR^{10}CO_2R^5)$,
 $-(N((C_1-C_4)alkyl))-D(COR^5)$, $-(N((C_1-C_4)alkyl))-D-Q$,
20 $-(N((C_1-C_4)alkyl))-D'-Q$ or Q radical;

wherein each R^{10} is independently a hydrogen or
 $(C_1-C_4)alkyl$ radical; or

- 25 X and A, when A is N, together with the adjoining
carbon atoms form a 5-membered to 10-membered mono- or
bicyclic heterocyclyl moiety which is optionally
substituted with 1-2 radicals of R^8 ;
- 30 Q is a 4-membered to 10-membered heterocyclyl or
heteroaryl ring optionally substituted with 1-2
radicals of R^8 ; wherein each R^8 is independently a $-OH$,
halo, $-CF_3$, $-OCF_3$, $(C_1-C_4)alkoxy$, $-NH_2$, $-NH((C_1-C_4)alkyl)$,
 $-N((C_1-C_4)alkyl)_2$, or $(C_1-C_4)alkyl$ radical;

444

each R^5 is independently a hydrogen, -OH, (C_1-C_4) alkoxy, -NH₂, -NH $((C_1-C_4)$ alkyl), -N $((C_1-C_4)$ alkyl)₂ or (C_1-C_4) alkyl radical;

- 5 D is $-(CH_2)_m((C_3-C_6)$ cycloalkyl)_k(CH₂)_m- and D' is $-((C_1-C_4)$ alkyl)_k-;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

- 10 each k is independently 0 or 1;
each m is independently an integer between 0 and 3;
each p is independently an integer between 0 and 2; and
each q is independently 1 or 2; and

- 15 wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R^2 , and R^3 is optionally substituted with 1-2 radicals of halo, -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂, (C_1-C_4) alkyl, (C_1-C_4) acyloxy, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹, -N(R⁹)₂, -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹ or
20 -S(O)₂ (C_1-C_4) alkyl, wherein each R⁹ is independently a hydrogen or (C_1-C_4) alkyl radical; and

- provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R^1 ,
25 R^2 and R^3 is 1-3;

or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

30

42. The method of claim 41, wherein Y is C(R⁶); A is O, S or N-H;

- R^6 is a hydrogen, -OH, chloro, fluoro, -CF₃, -OCF₃,
35 (C_1-C_2) alkoxy or (C_1-C_2) alkyl radical;

R^1 is a bromo, chloro, fluoro, -OH, -NO₂, -NHOH, -CF₃, -OCF₃, (C₁-C₂)alkyl, (C₁-C₂)alkoxy, -(NR¹⁰)_x((C₁-C₂)alkyl)_x-cyclopropyl, -NH₂ or -NH((C₁-C₂)alkyl) radical;

5

R^2 is a hydrogen, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₂)alkyl or (C₁-C₂)alkoxy radical;

R^3 is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl,

- 10 -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-,
 -((C₁-C₄)alkyl)N(R⁵)₂, -(CH₂)((C₅-C₆)cycloalkyl)_k(CH₂)_mOH,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mOH,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)OH,
 -(CH₂)((C₅-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₂)alkoxy,
 15 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(C₁-C₂)alkoxy,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)(C₁-C₂)alkoxy,
 -(CH₂)((C₅-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)N(R⁵)₂,
 20 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mS(O)_pR⁵,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(CO₂R⁵),
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(COR⁵), -D'(S(O)_qR⁵),
 -D'(aryloxy), -D'(aryl), -D'(heteroaryl),
 -D'((C₃-C₆)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl),
 25 -D(heteroaryl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂), -D(S(O)_qR⁵),
 -D(NR¹⁰CON(R⁵)₂), -D(NR¹⁰(CO)R⁵), -D(NR¹⁰CO₂R⁵) or -(NR¹⁰)_k-D-
 Q radical;

30 X is a -N((C₁-C₄)alkyl)₂ or 4-membered to 10-membered heterocyclyl or heteroaryl ring, having a nitrogen atom ring member bonded directly to the carbon atom adjoining X, optionally substituted with 1-2 radicals of R⁸;

35 wherein each R¹⁰ is independently a hydrogen or (C₁-C₂)alkyl radical; or

X and A, when A is N, together with the adjoining carbon atoms form a 8-membered to 10-membered bicyclic heterocyclyl moiety which is optionally substituted
 5 with 1-2 radicals of R⁸;

Q is a 4-membered to 10-membered heterocyclyl or heteroaryl ring optionally substituted with 1-2 radicals of R⁸; wherein each R⁸ is independently a -OH,
 10 halo, -CF₃, -OCF₃, (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl), -N((C₁-C₂)alkyl)₂, or (C₁-C₂)alkyl radical;

each R⁵ is independently a hydrogen, -OH, (C₁-C₂)alkoxy, -NH₂, -NH((C₁-C₂)alkyl), -N((C₁-C₂)alkyl)₂ or (C₁-C₂)alkyl
 15 radical;

D is -(CH₂)_m((C₅-C₆)cycloalkyl)_k(CH₂)_m- and D' is -((C₁-C₄)alkyl)_k-;

20 Z is (NR¹⁰)_kD or (NR¹⁰)_kD';

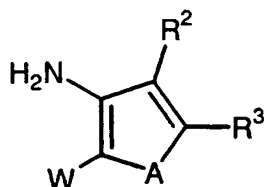
each k is independently 0 or 1;
 each m is independently an integer between 0 and 2;
 each p is independently an integer between 0 and 2; and
 25 each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of X, R² and R³ is optionally substituted with 1-2 radicals of halo, -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂,
 30 (C₁-C₄)alkyl, (C₁-C₄)acyloxy, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹, -N(R⁹)₂, -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹ or -S(O)₂(C₁-C₄)alkyl, wherein each R⁹ is independently a hydrogen or (C₁-C₂)alkyl radical; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, X, Y, R¹, R² and R³ is 1-2;

- 5 or a pharmaceutically acceptable salt, ester, solvate or N-oxide thereof.

43. A compound of formula



10

wherein A is O, S, S(O), S(O)₂, N-H, N-R⁴ or CR⁴R⁷; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

- 15 R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂), -Z(CO₂R⁵), -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵),
20 -Z(NR⁵CO₂R⁵), -Z(COR⁵), -Z(S(O)_pR⁵) or -Z(Q) radical;

- R³ is a (C₃-C₁₀)cycloalkyl, (C₁-C₈)alkyl, -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-, -((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl),
25 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_nOH, -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_nOH, -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)OH, -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy, -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy,
30 -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)(C₁-C₈)alkoxy, -(CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_nN(R⁵)₂, -(CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_nN(R⁵)₂,

$-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)N(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})cycloalkyl)(CH_2)_pS(O)_qR^5$, $-D'(S(O)_qR^5)$,
 $-D'(aryloxy)$, $-D'(aryl)$, $-D'(heteroaryl)$,
 $-D'((C_3-C_{10})cycloalkyl)$, $-D'(NR^5SO_2R^5)$, $-D'(CON(R^5)_2)$,
5 $-D'(CO_2R^5)$, $-D'(NR^5CON(R^5)_2)$, $-D'(NR^5(CO)R^5)$, $-D'(NR^5CO_2R^5)$,
 $-D'(COR^5)$, $-D'(Q)$, $-D(aryloxy)$, $-D(aryl)$,
 $-D(heteroaryl)$, $-D((C_3-C_{10})cycloalkyl)$, $-D(NR^5SO_2R^5)$,
 $-D(CON(R^5)_2)$, $-D(CO_2R^5)$, $-D(S(O)_qR^5)$, $-D(NR^5CON(R^5)_2)$,
 $-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$, $-D(COR^5)$ or $-(NR^5)_k-D-Q$
10 radical;

R^4 is a $(C_1-C_8)alkyl$, $(C_3-C_{10})cycloalkyl$,
 $-Z((C_1-C_8)alkoxy)$, $-Z(aryloxy)$, $-Z(aryl)$,
 $-Z(heteroaryl)$, $-Z((C_3-C_{10})cycloalkyl)$, $-Z(NR^5SO_2R^5)$,
15 $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$,
 $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$
radical;

Q is a 4-membered to 10-membered heterocyclyl or
20 heteroaryl ring optionally substituted with 1-2
radicals of R^8 ; wherein each R^8 is independently a $-OH$,
halo, $-CF_3$, $-OCF_3$, $(C_1-C_8)alkoxy$, $-NH_2$, $-NH((C_1-C_8)alkyl)$,
 $-N((C_1-C_8)alkyl)_2$, or $(C_1-C_8)alkyl$ radical;

25 each R^5 and R^7 are each independently a hydrogen, $-OH$,
 $(C_1-C_8)alkoxy$, aryl, $-NH_2$, $-NH((C_1-C_8)alkyl)$,
 $-N((C_1-C_8)alkyl)_2$, $(C_1-C_8)alkyl$ or $(C_3-C_{10})cycloalkyl$
radical;

30 D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is
 $-((C_1-C_8)alkyl)_k-$;

Z is $D(NR^5)_k$, $D'(NR^5)_k$, $(NR^5)_kD$ or $(NR^5)_kD'$;

35 each k is independently 0 or 1;

each m is independently an integer between 0 and 6;
 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and

- 5 wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q, alkoxy or aryloxy moiety of any of R², R³, R⁴, R⁵, R⁷ and R⁸ is optionally substituted with one or more radicals of halo, -CF₃, -OCF₃, -Z(COOH), -Z(OH), -Z(NO₂), -Z(SH), -Z((C₁-C₈)alkyl), -Z((C₁-C₈)acyloxy), -Z((C₃-C₁₀)cycloalkyl),
 10 -S-((C₁-C₈)alkyl)_x-aryl, -((C₁-C₈)alkyl)_x-SO₂NH-aryl, -S-(C₁-C₈)alkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁹SO₂R⁹), -Z(CON(R⁹)₂), -Z(CO₂R⁹), -Z(N(R⁹)₂), -Z(NR⁹CON(R⁹)₂), -Z(NR⁹(CO)R⁹), -Z(NR⁹CO₂R⁹), -Z(COR⁹),
 15 -Z(S(O)_pR⁹) or -Z(Q), wherein each R⁹ is independently a hydrogen or (C₁-C₈)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substituents are optionally substituted with one or more radicals of halo, -NO₂, -CF₃, -OCF₃, -N(R⁹)₂, -C(O)R⁹, -CO₂R⁹, -OR⁹,
 20 -SR⁹ or (C₁-C₈)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, R² and R³ is 0-3.

25

44. The compound of claim 43 wherein A is O, S, S(O), S(O)₂, N-H, N-R⁴ or CR⁴R⁷; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

30

- R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR⁵SO₂R⁵), -Z(CON(R⁵)₂),
 35 -Z(N(R⁵)₂), -Z(NR⁵CON(R⁵)₂), -Z(NR⁵(CO)R⁵), -Z(NR⁵CO₂R⁵), -Z(S(O)_pR⁵) or -Z(Q) radical;

- R^3 is a (C_3-C_{10}) cycloalkyl, (C_3-C_8) alkyl,
 $-((C_1-C_8)$ alkyl)OH, (C_1-C_8) alkoxy- (C_1-C_8) alkyl-,
 $-((C_1-C_8)$ alkyl) $N(R^5)_2$, $-((C_1-C_8)$ alkyl) $S(O)_p((C_1-C_8)$ alkyl),
 5 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m$ OH,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m$ OH,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m$ OH,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(C_1-C_8)$ alkoxy,
 10 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_m(C_1-C_8)$ alkoxy,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $_k(CH_2)_mN(R^5)_2$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_mS(O)_pR^5$,
 15 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(CO_2R^5)$,
 $-(CH_2)_m((C_3-C_{10})$ cycloalkyl) $(CH_2)_m(COR^5)$,
 $-((C_1-C_8)$ alkyl) (CO_2R^5) , $-((C_1-C_8)$ alkyl) (COR^5) ,
 $-D'(S(O)_pR^5)$, $-D'(\text{aryloxy})$, $-D'(\text{aryl})$, $-D'(\text{heteroaryl})$,
 $-D'((C_3-C_{10})$ cycloalkyl), $-D'(NR^5SO_2R^5)$, $-D'(CON(R^5)_2)$,
 20 $-D'(NR^5CON(R^5)_2)$, $-D'(NR^5(CO)R^5)$, $-D'(NR^5CO_2R^5)$, $-D'(Q)$,
 $-D(\text{aryloxy})$, $-D(\text{aryl})$, $-D(\text{heteroaryl})$,
 $-D((C_3-C_{10})$ cycloalkyl), $-D(NR^5SO_2R^5)$, $-D(CON(R^5)_2)$,
 $-D(S(O)_pR^5)$, $-D(NR^5CON(R^5)_2)$, $-D(NR^5(CO)R^5)$, $-D(NR^5CO_2R^5)$ or
 $-(NR^5)_k-D-Q$ radical;
 25
- R^4 is a (C_1-C_8) alkyl, (C_3-C_{10}) cycloalkyl,
 $-Z((C_1-C_8)$ alkoxy), $-Z(\text{aryloxy})$, $-Z(\text{aryl})$,
 $-Z(\text{heteroaryl})$, $-Z((C_3-C_{10})$ cycloalkyl), $-Z(NR^5SO_2R^5)$,
 $-Z(CON(R^5)_2)$, $-Z(CO_2R^5)$, $-Z(N(R^5)_2)$, $-Z(NR^5CON(R^5)_2)$,
 30 $-Z(NR^5(CO)R^5)$, $-Z(NR^5CO_2R^5)$, $-Z(COR^5)$, $-Z(S(O)_pR^5)$ or $-Z(Q)$
 radical;

Q is a 4-membered to 10-membered heterocyclyl or
 heteroaryl ring optionally substituted with 1-2
 35 radicals of R^8 ; wherein each R^8 is independently a -OH,

451

halo, $-\text{CF}_3$, $-\text{OCF}_3$, $(\text{C}_1\text{-C}_8)\text{alkoxy}$, $-\text{NH}_2$, $-\text{NH}((\text{C}_1\text{-C}_8)\text{alkyl})$,
 $-\text{N}((\text{C}_1\text{-C}_8)\text{alkyl})_2$, or $(\text{C}_1\text{-C}_8)\text{alkyl radical}$;

each R^5 and R^7 are each independently a hydrogen, $-\text{OH}$,
 5 $(\text{C}_1\text{-C}_8)\text{alkoxy}$, aryl, $-\text{NH}_2$, $-\text{NH}((\text{C}_1\text{-C}_8)\text{alkyl})$,
 $-\text{N}((\text{C}_1\text{-C}_8)\text{alkyl})_2$, $(\text{C}_1\text{-C}_8)\text{alkyl}$ or $(\text{C}_3\text{-C}_{10})\text{cycloalkyl}$
 radical;

D is $-(\text{CH}_2)_m((\text{C}_3\text{-C}_{10})\text{cycloalkyl})_k(\text{CH}_2)_m-$ and D' is
 10 $-(\text{C}_1\text{-C}_8)\text{alkyl})_k-$;

Z is $\text{D}(\text{NR}^5)_k$, $\text{D}'(\text{NR}^5)_k$, $(\text{NR}^5)_k\text{D}$ or $(\text{NR}^5)_k\text{D}'$;

each k is independently 0 or 1;
 15 each m is independently an integer between 0 and 6;
 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and

wherein each alkyl, aryl, heteroaryl, cycloalkyl, Q,
 20 alkoxy or aryloxy moiety of any of R^2 , R^3 , R^4 , R^5 and R^7
 is optionally substituted with 1-3 radicals of halo and
 1-2 radicals of $-\text{CF}_3$, $-\text{OCF}_3$, $-\text{Z}(\text{COOH})$, $-\text{Z}(\text{OH})$, $-\text{Z}(\text{NO}_2)$,
 $-\text{Z}(\text{SH})$, $-(\text{C}_1\text{-C}_8)\text{alkyl}$, $-(\text{C}_1\text{-C}_8)\text{acyloxy}$,
 $-(\text{C}_3\text{-C}_{10})\text{cycloalkyl}$, $-\text{S}-((\text{C}_1\text{-C}_8)\text{alkyl})_k\text{-aryl}$,
 25 $-(\text{C}_1\text{-C}_8)\text{alkyl})_k\text{-SO}_2\text{NH-aryl}$, $-\text{S}-(\text{C}_1\text{-C}_8)\text{alkyl}$,
 $-\text{Z}((\text{C}_1\text{-C}_8)\text{alkoxy})$, $-\text{Z}(\text{aryloxy})$, $-\text{Z}(\text{aryl})$,
 $-\text{Z}(\text{heteroaryl})$, $-\text{Z}((\text{C}_3\text{-C}_{10})\text{cycloalkyl})$, $-\text{Z}(\text{NR}^9\text{SO}_2\text{R}^9)$,
 $-\text{Z}(\text{CON}(\text{R}^9)_2)$, $-\text{Z}(\text{CO}_2\text{R}^9)$, $-\text{Z}(\text{N}(\text{R}^9)_2)$, $-\text{Z}(\text{NR}^9\text{CON}(\text{R}^9)_2)$,
 $-\text{Z}(\text{NR}^9(\text{CO})\text{R}^9)$, $-\text{Z}(\text{NR}^9\text{CO}_2\text{R}^9)$, $-\text{Z}(\text{COR}^9)$, $-\text{Z}(\text{S}(\text{O})_p\text{R}^9)$ or
 30 $-\text{Z}(\text{Q})$, wherein each R^9 is independently a hydrogen or
 $(\text{C}_1\text{-C}_8)\text{alkyl radical}$ and wherein such aryl, heteroaryl,
 cycloalkyl and Q substituents are optionally
 substituted with 1-3 radicals of halo, $-\text{NO}_2$, $-\text{CF}_3$,
 $-\text{OCF}_3$, $-\text{N}(\text{R}^9)_2$, $-\text{C}(\text{O})\text{R}^9$, $-\text{CO}_2\text{R}^9$, $-\text{OR}^9$, $-\text{SR}^9$ or $(\text{C}_1\text{-C}_8)\text{alkyl}$.

35

45. The compound of claim 44 wherein A is O, S, N-H or N-R⁴; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

5

R² is a hydrogen, halo, -OH, -NO₂, -CF₃, -OCF₃, (C₁-C₈)alkyl, (C₃-C₁₀)cycloalkyl, -Z((C₁-C₈)alkoxy), -Z(aryloxy), -Z(aryl), -Z(heteroaryl), -Z((C₃-C₁₀)cycloalkyl), -Z(NR¹⁰SO₂R⁵), -Z(CON(R⁵)₂),
 10 -Z(N(R⁵)₂), -Z(NR¹⁰CON(R⁵)₂), -Z(NR¹⁰(CO)R⁵), -Z(NR¹⁰CO₂R⁵), -Z(S(O)_pR⁵) or -Z(Q) radical, provided that R² is not an optionally substituted aryl or heteroaryl radical;

R³ is a (C₃-C₁₀)cycloalkyl, (C₃-C₈)alkyl,
 15 -((C₁-C₈)alkyl)OH, (C₁-C₈)alkoxy-(C₁-C₈)alkyl-, -((C₁-C₈)alkyl)N(R⁵)₂, -((C₁-C₈)alkyl)S(O)_p((C₁-C₈)alkyl), - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mOH, - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mOH, - (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)OH,
 20 - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy, - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(C₁-C₈)alkoxy, - (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_m(C₁-C₈)alkoxy, - (CH₂)_k((C₃-C₁₀)cycloalkyl)_k(CH₂)_mN(R⁵)₂, - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mN(R⁵)₂,
 25 - (CH₂)_m((C₃-C₁₀)cycloalkyl)_k(CH₂)_mN(R⁵)₂, - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_mS(O)_pR⁵, - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(CO₂R⁵), - (CH₂)_m((C₃-C₁₀)cycloalkyl)(CH₂)_m(COR⁵), - ((C₁-C₈)alkyl)(CO₂R⁵), - ((C₁-C₈)alkyl)(COR⁵),
 30 -D'(S(O)_pR⁵), -D'(aryloxy), -D'(aryl), -D'(heteroaryl), -D'((C₃-C₁₀)cycloalkyl), -D'(NR¹⁰SO₂R⁵), -D'(CON(R⁵)₂), -D'(NR¹⁰CON(R⁵)₂), -D'(NR¹⁰(CO)R⁵), -D'(NR¹⁰CO₂R⁵), -D'(Q), -D(aryloxy), -D(aryl), -D(heteroaryl), -D((C₃-C₁₀)cycloalkyl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂),
 35 -D(S(O)_pR⁵), -D(NR¹⁰CON(R⁵)₂), -D(NR¹⁰(CO)R⁵), -D(NR¹⁰CO₂R⁵) or - (NR¹⁰)_k-D-Q radical, provided R³ is not -SO₂NH₂;

R^4 is a (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, $-N(R^5)_2$ or $-Z(Q)$ radical;

- 5 wherein each R^{10} is independently a hydrogen or (C_1-C_4) alkyl radical; or

Q is a 4-membered to 10-membered heterocyclcyl or heteroaryl ring optionally substituted with 1-2
 10 radicals of R^8 ; wherein each R^8 is independently a $-OH$, halo, $-CF_3$, $-OCF_3$, (C_1-C_4) alkoxy, $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, or $(C_1-C_4)alkyl$ radical;

each R^5 is independently a hydrogen, $-OH$, (C_1-C_4) alkoxy,
 15 $-NH_2$, $-NH((C_1-C_4)alkyl)$, $-N((C_1-C_4)alkyl)_2$, $(C_1-C_4)alkyl$ or (C_3-C_6) cycloalkyl radical;

D is $-(CH_2)_m((C_3-C_{10})cycloalkyl)_k(CH_2)_m-$ and D' is $-((C_1-C_8)alkyl)_k-$;

20

Z is $D(NR^{10})_k$, $D'(NR^{10})_k$, $(NR^{10})_kD$ or $(NR^{10})_kD'$;

each k is independently 0 or 1;

each m is independently an integer between 0 and 4;

- 25 each p is independently an integer between 0 and 2; and
 each q is independently 1 or 2; and

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy moiety of any of R^2 , R^3 , R^4 and R^5 is optionally
 30 substituted with 1-3 radicals of halo and 1-2 radicals of $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $-(C_1-C_4)alkyl$, $-(C_1-C_4)acyloxy$, $-(C_3-C_6)cycloalkyl$, $-S-((C_1-C_4)alkyl)_k-aryl$, $-((C_1-C_4)alkyl)_k-SO_2NH-aryl$, aryloxy, aryl, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$,
 35 $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$, $-S(O)_2(C_1-C_4)alkyl$ or Q, wherein each R^9 is independently

a hydrogen or (C₁-C₄)alkyl radical and wherein such aryl, heteroaryl, cycloalkyl and Q substituents are optionally substituted with 1-2 radicals of halo, -NO₂, -CF₃, -OCF₃, -N(R⁹)₂, -C(O)R⁹, -CO₂R⁹, -OR⁹, -SR⁹ or

5. (C₁-C₄)alkyl; and

provided that the total number of aryl, heteroaryl, cycloalkyl, heterocyclyl and Q moieties in A, R² and R³ is 0-2.

10

46. The compound of claim 45 wherein A is O, S, N-H or N-R⁴; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

15

R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃, (C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(C₁-C₄)alkoxy, -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(CON(R⁵)₂), -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(N(R⁵)₂), -(NR¹⁰)_k((C₁-C₂)alkyl)_k-(S(O)_pR⁵) or -(NR¹⁰)_k((C₁-C₂)alkyl)_k-Q radical;

20

R³ is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl, -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-, -((C₁-C₄)alkyl)N(R⁵)₂, -(CH₂)_k((C₃-C₆)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mOH, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)OH, -(CH₂)_k((C₃-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₄)alkoxy, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_m(C₁-C₄)alkoxy, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)(C₁-C₄)alkoxy, -(CH₂)_k((C₃-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mN(R⁵)₂, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)N(R⁵)₂, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_mS(O)_pR⁵, -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_m(CO₂R⁵), -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_m(COR⁵), -D'(S(O)_qR⁵), -D'(aryloxy), -D'(aryl), -D'(heteroaryl),

25

30

35

-D'((C₃-C₁₀)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl),
 -D(heteroaryl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂), -D(S(O)_qR⁵),
 -D(NR¹⁰CON(R⁵)₂), -D(NR¹⁰(CO)R⁵), -D(NR¹⁰CO₂R⁵) or -(NR¹⁰)_k-D-
 Q radical, provided R³ is not -SO₂NH₂;

5

R⁴ is a (C₁-C₄)alkyl radical;

wherein each R¹⁰ is independently a hydrogen or
 (C₁-C₄)alkyl radical; or

10

Q is a 4-membered to 10-membered heterocyclcyl or
 heteroaryl ring optionally substituted with 1-2
 radicals of R⁸; wherein each R⁸ is independently a -OH,
 halo, -CF₃, -OCF₃, (C₁-C₄)alkoxy, -NH₂, -NH((C₁-C₄)alkyl),
 15 -N((C₁-C₄)alkyl)₂, or (C₁-C₄)alkyl radical;

each R⁵ is independently a hydrogen, -OH, (C₁-C₄)alkoxy,
 -NH₂, -NH((C₁-C₄)alkyl), -N((C₁-C₄)alkyl)₂ or (C₁-C₄)alkyl
 radical;

20

D is -(CH₂)_m((C₃-C₆)cycloalkyl)_k(CH₂)_n- and D' is
 -((C₁-C₄)alkyl)_k-;

Z is (NR¹⁰)_kD or (NR¹⁰)_kD';

25

each k is independently 0 or 1;

each m is independently an integer between 0 and 3;

each p is independently an integer between 0 and 2; and

each q is independently 1 or 2; and

30

wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy
 moiety of any of R² and R³ is optionally substituted
 with 1-2 radicals of halo, -CF₃, -OCF₃, -OR⁹, -SR⁹, -NO₂,
 (C₁-C₄)alkyl, (C₁-C₄)acyloxy, -NR⁹SO₂R⁹, -CON(R⁹)₂, -CO₂R⁹,
 35 -N(R⁹)₂, -NR⁹CON(R⁹)₂, -NR⁹(CO)R⁹, -NR⁹CO₂R⁹, -COR⁹ or

-S(O)₂(C₁-C₄)alkyl, wherein each R⁹ is independently a hydrogen or (C₁-C₄)alkyl radical; and

provided that the total number of aryl, heteroaryl,
 5 cycloalkyl, heterocyclyl and Q moieties in A, R² and R³ is 0-1.

47. The compound of claim 46 wherein wherein A is
 10 O, S or N-H; W is -CN or -C(O)L; wherein L is a halo or C1-C2 alkoxy radical;

R² is a hydrogen, chloro, fluoro, -CF₃, -OCF₃,
 (C₁-C₂)alkyl or (C₁-C₂)alkoxy radical;

15

R³ is a (C₃-C₆)cycloalkyl, (C₃-C₆)alkyl,
 -((C₁-C₄)alkyl)OH, (C₁-C₄)alkoxy-(C₁-C₄)alkyl-,
 -((C₁-C₄)alkyl)N(R⁵)₂, -(CH₂)((C₅-C₆)cycloalkyl)_x(CH₂)_mOH,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mOH,

20

-(CH₂)_m((C₅-C₆)cycloalkyl)_x(CH₂)OH,
 -(CH₂)((C₅-C₆)cycloalkyl)_x(CH₂)_m(C₁-C₂)alkoxy,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(C₁-C₂)alkoxy,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_x(CH₂)(C₁-C₂)alkoxy,
 -(CH₂)((C₅-C₆)cycloalkyl)_x(CH₂)_mN(R⁵)₂,

25

-(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mN(R⁵)₂,
 -(CH₂)_m((C₅-C₆)cycloalkyl)_x(CH₂)N(R⁵)₂,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_mS(O)_pR⁵,
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(CO₂R⁵),
 -(CH₂)_m((C₅-C₆)cycloalkyl)(CH₂)_m(COR⁵), -D'(S(O)_qR⁵),

30

-D'(aryloxy), -D'(aryl), -D'(heteroaryl),
 -D'((C₃-C₆)cycloalkyl), -D'(Q), -D(aryloxy), -D(aryl),
 -D(heteroaryl), -D(NR¹⁰SO₂R⁵), -D(CON(R⁵)₂), -D(S(O)_qR⁵),
 -D(NR¹⁰CON(R⁵)₂), -D(NR¹⁰(CO)R⁵), -D(NR¹⁰CO₂R⁵) or -(NR¹⁰)_x-D-
 Q radical, provided R³ is not -SO₂NH₂;

35

wherein each R^{10} is independently a hydrogen or (C_1-C_2) alkyl radical; or

- Q is a 4-membered to 10-membered heterocyclcyl or
 5 heteroaryl ring optionally substituted with 1-2 radicals of R^8 ; wherein each R^8 is independently a -OH, halo, $-CF_3$, $-OCF_3$, (C_1-C_2) alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$, or $(C_1-C_2)alkyl$ radical;
- 10 each R^5 is independently a hydrogen, -OH, (C_1-C_2) alkoxy, $-NH_2$, $-NH((C_1-C_2)alkyl)$, $-N((C_1-C_2)alkyl)_2$ or $(C_1-C_2)alkyl$ radical;

- D is $-(CH_2)_m((C_5-C_6)cycloalkyl)_k(CH_2)_n-$ and D' is
 15 $-((C_1-C_4)alkyl)_k-$;

Z is $(NR^{10})_kD$ or $(NR^{10})_kD'$;

- each k is independently 0 or 1;
- 20 each m is independently an integer between 0 and 2;
- each p is independently an integer between 0 and 2; and
- each q is independently 1 or 2; and

- wherein each aryl, heteroaryl, cycloalkyl, Q or aryloxy
 25 moiety of R^3 is optionally substituted with 1-2 radicals of halo, $-CF_3$, $-OCF_3$, $-OR^9$, $-SR^9$, $-NO_2$, $(C_1-C_4)alkyl$, $(C_1-C_4)acyloxy$, $-NR^9SO_2R^9$, $-CON(R^9)_2$, $-CO_2R^9$, $-N(R^9)_2$, $-NR^9CON(R^9)_2$, $-NR^9(CO)R^9$, $-NR^9CO_2R^9$, $-COR^9$ or $-S(O)_2(C_1-C_4)alkyl$, wherein each R^9 is independently a
 30 hydrogen or $(C_1-C_2)alkyl$ radical.

Fig. 1A

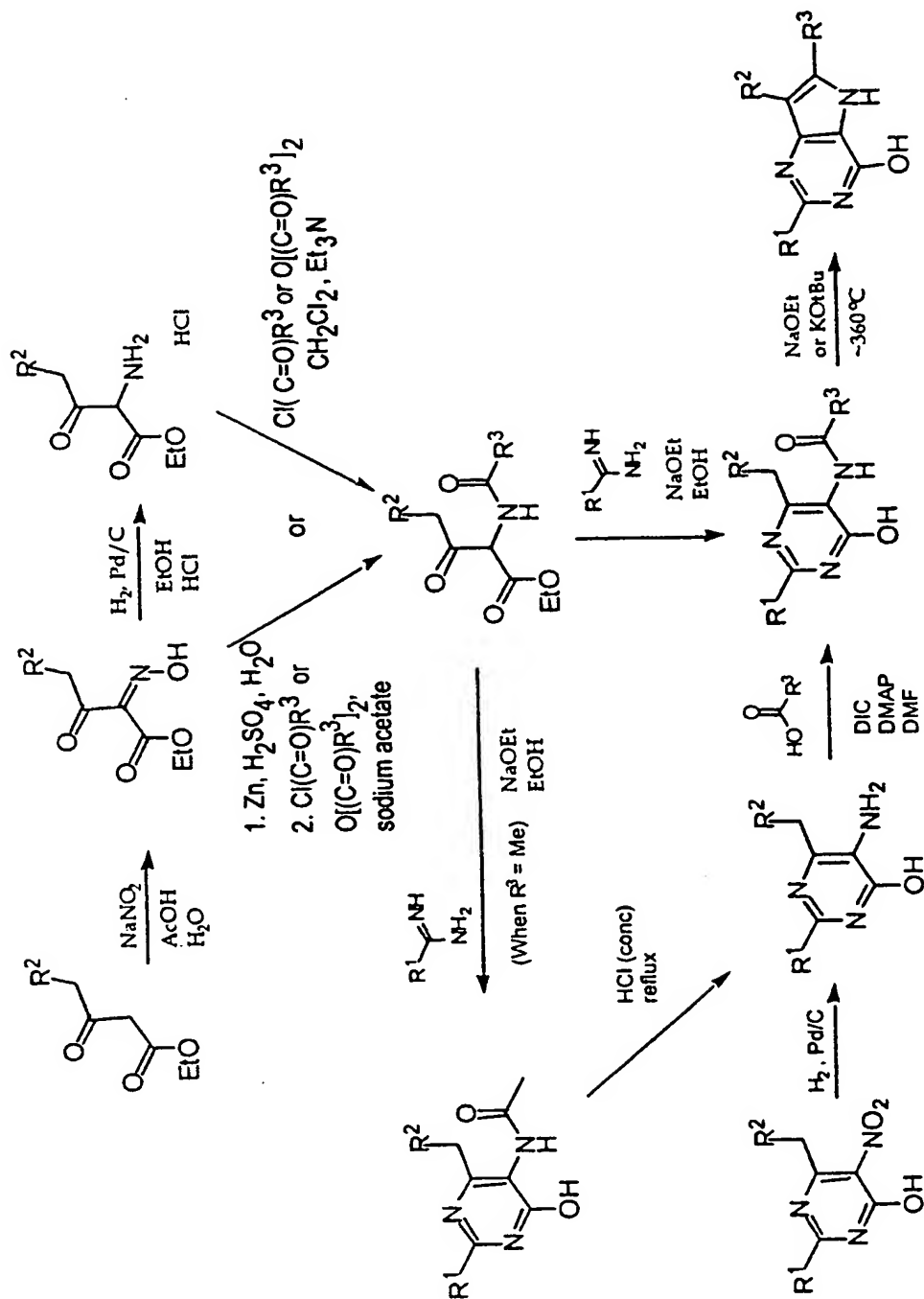


Fig. 1B

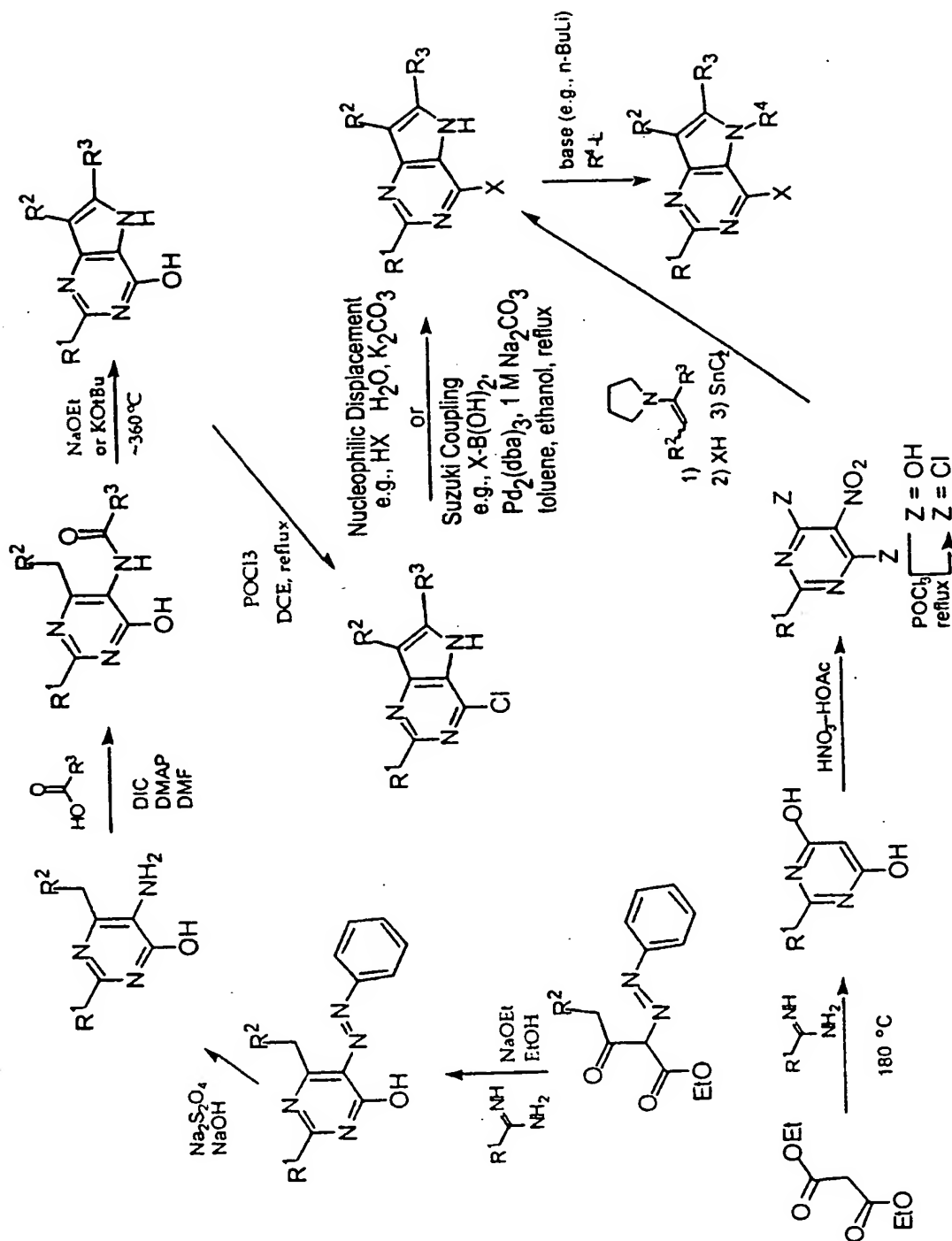


Fig. 2

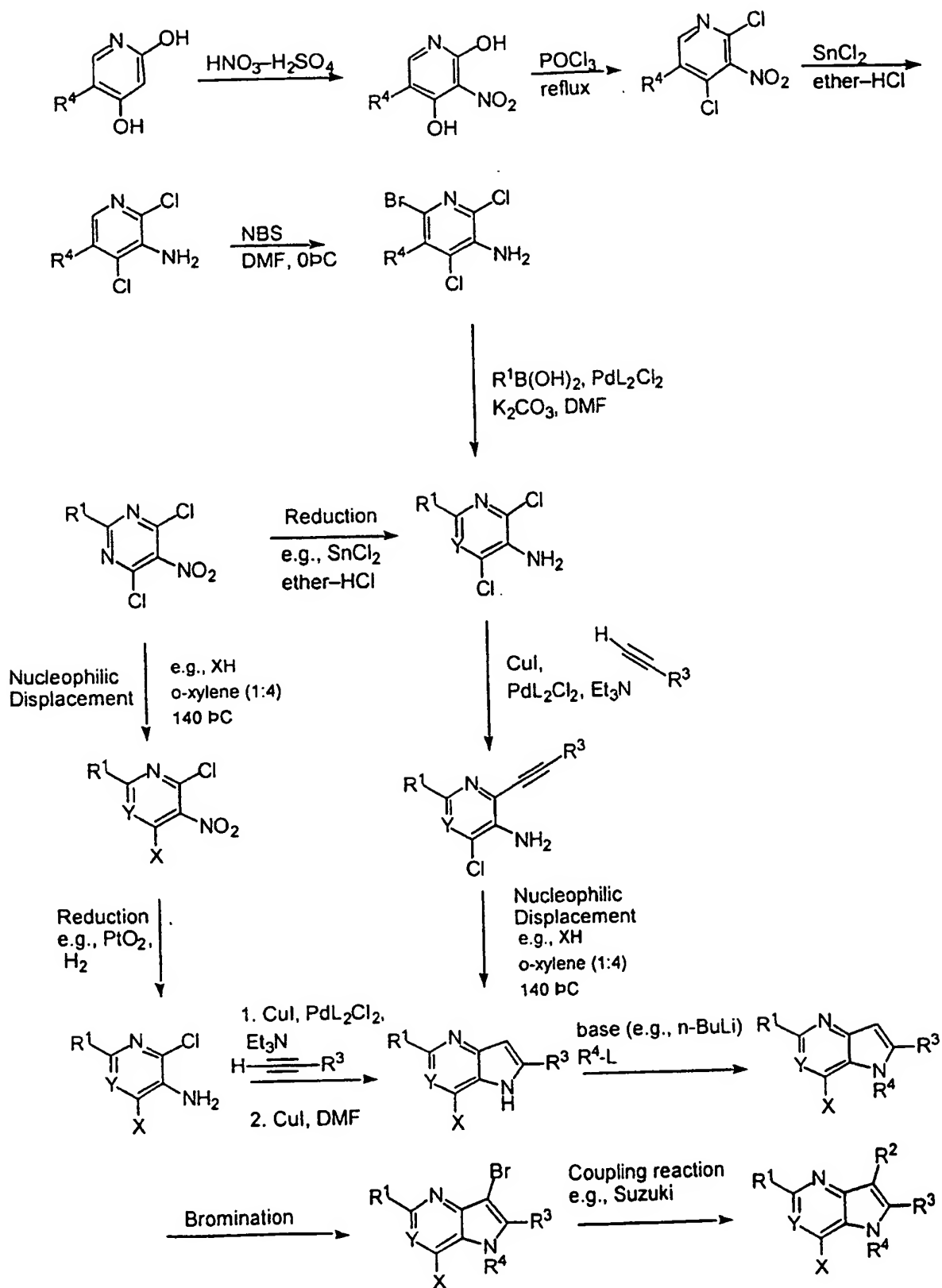


Fig. 3

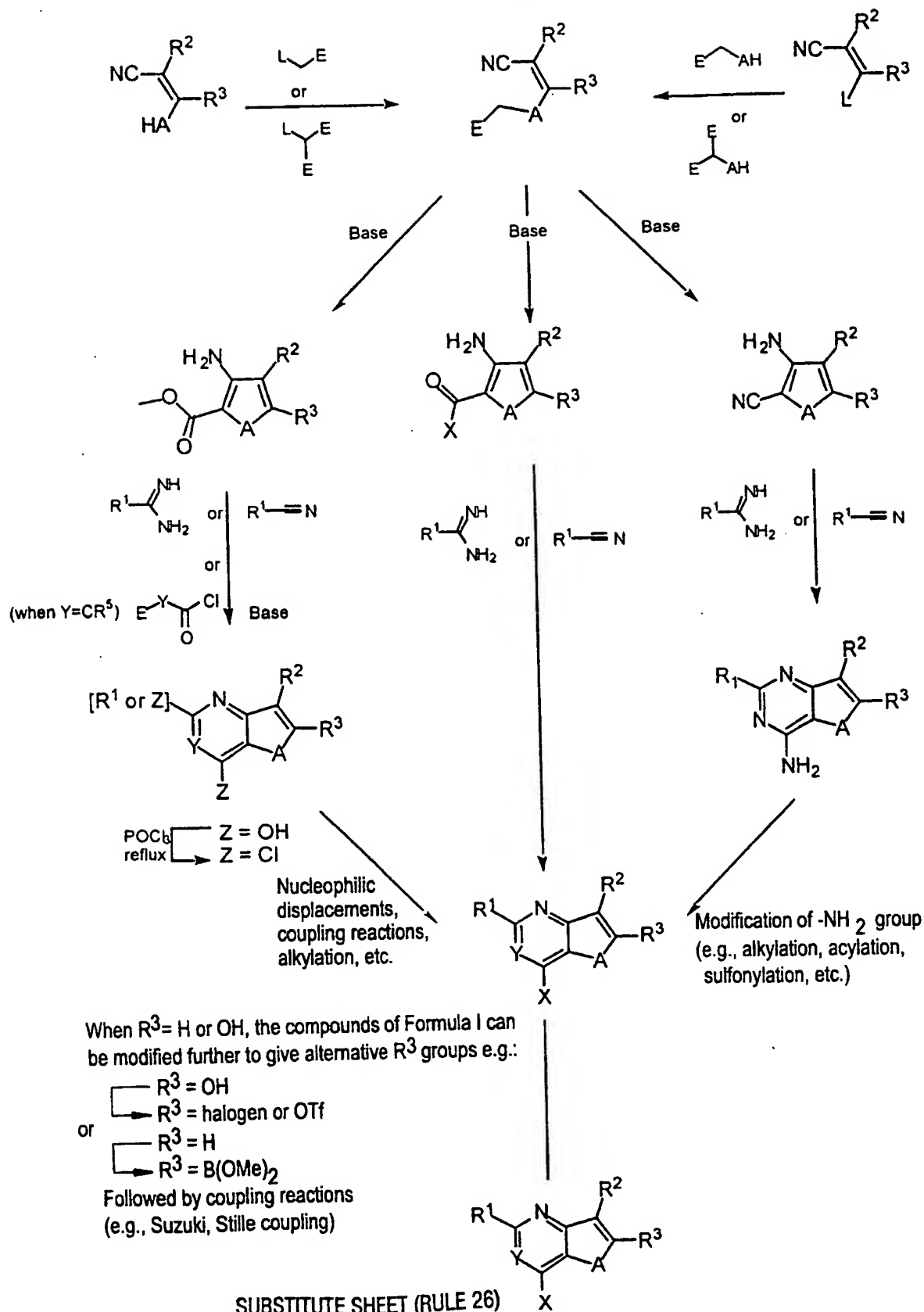
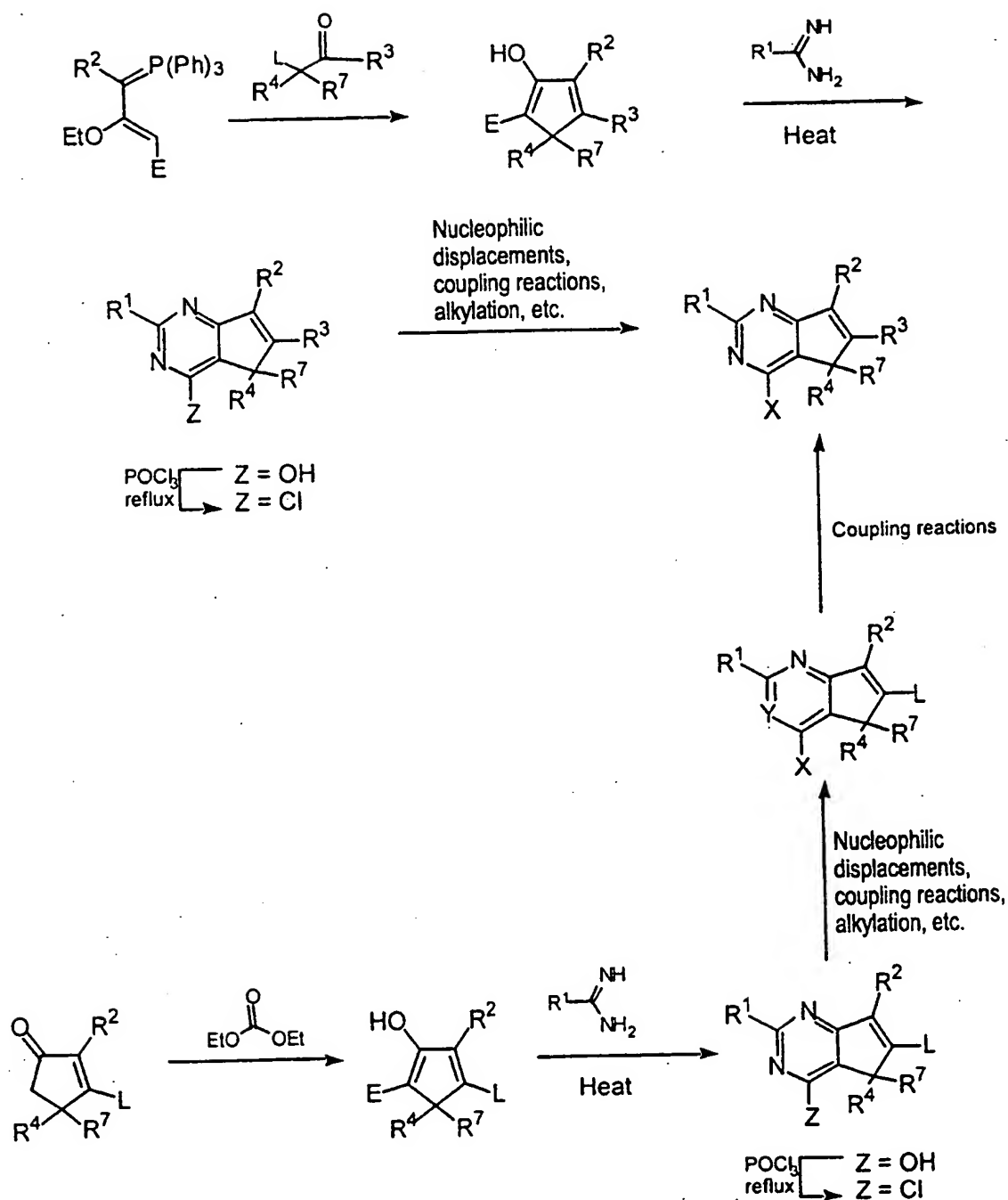


Fig. 4



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/02500

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D471/04 A61K31/44 A61K31/505 A61K31/52 C07D487/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 29110 A (JANSSEN PHARMACEUTICA N. V.) 14 August 1997 cited in the application see the whole document ---	1,19,43
Y	WO 97 25041 A (ELI LILLY AND COMPANY) 17 July 1997 see the whole document ---	1,19,43
Y	WO 96 40142 A (PFIZER INC.) 19 December 1996 see page 2, line 30 - page 5, line 30 ---	1,19
Y	WO 96 35689 A (NEUROGEN CORPORATION) 14 November 1996 cited in the application see page 2 - page 3 ---	1,19
	-/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

7 June 1999

Date of mailing of the international search report

15/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kyriakakou, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/02500

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 778 277 A (PFIZER INC.) 11 June 1997 see the whole document ----	1,19,43
Y	EP 0 729 758 A (PFIZER INC.) 4 September 1996 see the whole document ----	1,19
Y	EP 0 682 027 A (CIBA-GEIGY AG) 15 November 1995 see the whole document ----	1,19,43
P,A	WO 98 07726 A (NOVARTIS AG) 26 February 1998 cited in the application see the whole document ----	1,19
P,A	WO 98 08847 A (PFIZER INC.) 5 March 1998 cited in the application see the whole document ----	1,19,43
P,A	WO 98 06703 A (WARNER-LAMBERT COMPANY) 19 February 1998 cited in the application see the whole document -----	1,19

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter national Application No

PCT/US 99/02500

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9729110 A	14-08-1997	AU 1720997 A CA 2233307 A EP 0882051 A NO 981356 A	28-08-1997 14-08-1997 09-12-1998 09-07-1998
WO 9725041 A	17-07-1997	AU 2242197 A CA 2242579 A EP 0871442 A	01-08-1997 17-07-1997 21-10-1998
WO 9640142 A	19-12-1996	CA 2223081 A HU 9601559 A AP 637 A AU 5479196 A BR 9602695 A CN 1141298 A CZ 9601641 A EP 0831829 A FI 974443 A HR 960269 A JP 10508875 T NO 962386 A NZ 286755 A PL 314641 A SG 45483 A SI 9600184 A SK 72996 A	19-12-1996 28-02-1997 08-04-1998 19-12-1996 06-10-1996 29-01-1997 11-12-1996 01-04-1998 05-12-1997 31-08-1997 02-09-1998 09-12-1996 25-03-1998 09-12-1996 16-01-1998 30-04-1997 09-04-1997
WO 9635689 A	14-11-1996	US 5804685 A US 5644057 A AU 5679096 A CA 2194756 A EP 0770080 A JP 10506126 T US 5847136 A	08-09-1998 01-07-1997 29-11-1996 14-11-1996 02-05-1997 16-06-1998 08-12-1998
EP 778277 A	11-06-1997	CA 2192289 A JP 9188682 A	09-06-1997 22-07-1997
EP 729758 A	04-09-1996	AU 4585996 A CA 2170700 A CN 1141297 A JP 8259567 A	12-09-1996 03-09-1996 29-01-1997 08-10-1996
EP 682027 A	15-11-1995	AT 159257 T AU 695244 B AU 1772295 A CA 2148324 A CN 1128263 A CZ 9501131 A DE 59500788 D DK 682027 T ES 2109796 T FI 952033 A GR 3025158 T HK 1002935 A HU 71818 A JP 8053454 A NO 951684 A	15-11-1997 13-08-1998 09-11-1995 04-11-1995 07-08-1996 13-12-1995 20-11-1997 04-05-1998 16-01-1998 04-11-1995 27-02-1998 25-09-1998 28-02-1996 27-02-1996 06-11-1995

INTERNATIONAL SEARCH REPORT

In ...national application No.

PCT/US 99/ 02500

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 27-42
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 27-42
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 99/02500

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 682027 A		NZ 272031 A PL 308426 A SK 56195 A US 5686457 A ZA 9503495 A	29-01-1997 13-11-1995 08-05-1996 11-11-1997 03-11-1995
WO 9807726 A	26-02-1998	AU 4206497 A	06-03-1998
WO 9808847 A	05-03-1998	AU 3456197 A HR 970454 A NO 990927 A	19-03-1998 31-08-1998 26-02-1999
WO 9806703 A	19-02-1998	AU 4054197 A	06-03-1998